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STUDIES ON THE NORMAL AND PATHOLOGICAL HISTOLOGY OF THE LUNG [1]

WILLIAM SNOW MILLER

From various studies on the normal and pathological histology of the lung I have selected the ultimate arrangement of the air-spaces and the distribution of smooth muscle for my topics on the normal side, and the relation of reticulum to the tuberculous processes occurring in the human lung, on the pathological side.

It would be interesting to follow the gradual evolution of our present conception of the ultimate arrangement of the air-spaces did time permit. I can discuss only some of the more salient points.

In 1661 Malpighi showed that the conception of the lung being composed of "spumous blood or bloody spume," as described by Vesalius, was erroneous, and that the air and blood were contained in separate vessels. He also showed that the lung had a cellular structure.

Passing over the work of Willis, Reisseisen, von Sömmering, Moleschott, and other worthy investigators, we come to the year 1846, in which Rossignol described the lungs as being formed of successive bronchial ramifications which terminated by suddenly dilating into the form of funnels (*infundibula*), the internal walls of which were lined with alveoli. Alveoli also lined the last two or three divisions of the bronchial tubes. The introduction of the term *infundibulum* was unfortunate, for this misnomer has occasioned much confusion in interpreting the structure of the lung.

Rossignol defines an infundibulum as "a small sac, more or less conical in shape, having its internal surface partitioned off by numerous alveoli, and having but a single opening of communication with the external air" (fig. 1). Along the bronchial tubes his alveoli were formed by partitions projecting into their lumina and not, as is now known, by evaginations from their surface. His conception of there being only one communication between an infundibulum and the external air was correct; but his conception of the relation which the infundibula bore to the last division of the bronchial tree was incorrect.

[1] A lecture given before the Harvey Society, New York, October 25, 1924.

In 1852 Kölliker published the first edition of his *Mikroskopische Anatomie*. The scheme which he there gave (fig. 2) of the air-spaces connected with the last division of the bronchial tree is familiar to the older members of this Society, and is even now occasionally republished. In the preceding scheme of Rossignol the last division of the bronchial tree terminated in an infundibulum, which often showed a partial subdivision. In the scheme of Kölliker the last division of the bronchial tree terminated in a pyriform *sacculus*, which had opening into it a group of air-cells, or pulmonary vesicles. Because of this grouping of the vesicles, which he compared to the lobules of a racemous gland, he said that there was no occasion to designate them infundibula, as was done by Rossignol. On the other hand, the sacculi of Kölliker and the infundibula of Rossignol are identical and constitute the finest lobules (*primary lobules*) in contradistinction to the *secondary lobules*, which were composed of a variable number of primary lobules and were marked out by connective-tissue septa. The alveoli of the infundibulum of Rossignol always opened directly into it, while the alveoli of Kölliker did not always open directly into a sacculus, but opened first into other alveoli and through them into the common cavity of the sacculus.

In 1860 the Fothergillian Gold Medal was awarded to A. T. Houghton Waters for his essay on *The Anatomy of the Human Lung*. This is the most exhaustive and accurate piece of work which had been done on the lung up to that time and, had modern methods of reconstruction been available, he would, no doubt, have been able to solve the perplexing problem of the structure of the lung.

According to Rossignol and to Kölliker the last division of the bronchial tree ended in a single cavity, called by the former an *infundibulum*, by the latter a *sacculus*. Waters rejects all previous nomenclature and calls the last division of the bronchial tree a *terminal bronchial tube;* sometimes he uses as a synonym *ultimate bronchial tube*. The large air-spaces connected with a terminal bronchial tube he calls *air-sacs;* the small projections from the surface of the terminal bronchial tubes and from the air-sacs he calls *alveoli*, a term first used by Rossignol. It is from his nomenclature that *terminal bronchus* and *air-sac* have passed into common usage in English and American descriptions of pulmonary structure.

While in the schemes of Rossignol and of Kölliker only a single air-sac was connected with the last division of the bronchial tree, Waters found that a group of air-sacs was connected with each terminal bronchial tube.

These air-sacs did not communicate with each other; neither did the group of air-sacs that were connected with one terminal bronchial tube communicate with those of an adjoining group. Sometimes an air-sac would present a deep cleft on its more distal margin, indicating a partial subdivision (fig. 3).

Waters introduced the term *lobulette* (little lobule) in the place of lobule, to designate the group of air-sacs connected with the terminal bronchial tube. This did not meet with favor; the term *lobule* has been retained and has its original significance, that is, *the last division of the bronchial tree and the air-spaces connected with it.*

In tracing the course of the air-sacs Waters found that, as they pass from the periphery of the lobule, they diminish in size and eventually open into the dilated end of a terminal bronchial tube. Sometimes two or three air-sacs joined together before opening into the dilated end of a terminal bronchial tube which he calls the *point de réunion* of all the air-sacs.

Alveoli were, according to Waters, present not only over the surface of the air-sacs, but also along the terminal bronchial tube. Rossignol called special attention to the alveoli in this situation. He found them along the last two or three divisions of the bronchial tree. Waters could only demonstrate them on his terminal bronchial tube, and thought it possible that Rossignol drew his conclusions from observations on the cat's lung in which, he says, they are more abundant than in the human lung. Rossignol was right in his statement, however, as reconstruction methods have demonstrated.

The diagram of F. E. Schulze (fig. 4) is still used by many of the Continental writers to explain the normal and pathological histology of the lung. In order to obtain an intelligent understanding of this diagram it will be necessary to follow closely his description.

Each lung, he says, is supplied with a single bronchus which, as soon as it has penetrated into the substance of the lung, breaks up into a series of dichotomous branches which pursue a straight course until they reach a position near the surface of the lung. Each of these branches gives off laterally, in a spiral manner, still smaller branches, which also have a straight course. The lateral branches to which these smaller branches give origin break up into terminal branches which again have a straight course. By this mode of branching the smallest bronchi take a peculiar zigzag course. The smallest of the above series of branches (fig. 4, *a*) terminate in the respiratory cavities. These

cavities also consist of round tubes which break up, by a dichotomous method of division, into two to four terminal twigs which again have short lateral branches. The terminal twigs and their lateral branches end in a blind, funnel-shaped cavity, which Schulze calls an *infundibulum.*

The course of these various divisions of the original bronchus is indeed a zigzag one; but we eventually arrive at the same type of ending as in the earlier schemes (Waters excepted), namely, an infundibulum.

The cylindrical passages which are situated between the last of the bronchial subdivisions and the infundibula do not have smooth walls, but are lined with numerous alveoli. For this reason Schulze has named them *alveolar passages* (*Alveolengänge*).

For the first time we have a name for that subdivision of the bronchial tree which possesses alveoli and is situated between the last bronchial tube with smooth walls and an infundibulum. This constitutes the contribution of Schulze to our knowledge of pulmonary architecture. In his study of the histological structure of the lung he made other and valuable contributions, some of which will be discussed in connection with my second topic.

In 1881 Kölliker again studied the structure of the lung, mainly in connection with its epithelium. We have seen that Schulze gave the name *alveolar passage* to the long cylindrical tube, beset on all sides with alveoli and situated between a smooth bronchial tube and an infundibulum. Kölliker goes a step further, and divides this long alveolar passage (*Alveolargang*) into two parts, depending on the type of the epithelium. That part which is situated more deeply in the substance of the lung he named *bronchiolus respiratorius* (respiratory bronchiole), because it took part in respiration; while for that part which was directly connected with an infundibulum he retained the name introduced by Schulze, *Alveolargang* (*alveolar passage*). Both of these subdivisions possess alveoli, but they are more abundant along the alveolar passage.

Before proceeding further we may bring together the various points which the investigators under consideration have worked out. Rossignol showed that after various subdivisions the bronchial tubes terminated in a funnel-shaped dilatation which he called an *infundibulum*, and that alveoli were present along the last two or three divisions of the bronchial tree. Kölliker did not add, at this time, anything of importance to the architecture of the lung. He confirmed in nearly every point the work of Rossignol. He did add to our knowledge of the histological

structure of various parts of the lungs; but this is foreign to our subject. Waters made a very material addition to our knowledge in showing that a number of air-sacs (infundibula) were connected with each terminal bronchial tube. Schulze ignored the work of Waters, and returned to the idea of a single infundibulum forming the ultimate ending of each bronchial tube. He gave a name (*Alveolargang*) to the divisions of the bronchial tree first described by Rossignol as possessing alveoli. Finally Kölliker subdivided the *Alveolargang* of Schulze into two parts, *bronchiolus respiratorius* and *Alveolargang*, and this latter name was changed to *ductulus alveolaris* when the *B. N. A.* nomenclature came into use (1895).

We now have the following nomenclature for the last divisions of the bronchial tree: *bronchiolus; bronchiolus respiratorius; Alveolargang;* and a group of elongated, more or less funnel-shaped *infundibula* or *air-sacs*, attached to its distal end. It remains to be seen whether these groups of elongated infundibula cannot be further subdivided.

In the early part of 1887 I spent some time working in the Pathological Laboratory of the College of Physicians and Surgeons, New York. At that time Professor Delafield was supporting, in the face of much opposition, the thesis that there existed intercommunication between the air-vesicles. The opportunity came to me, shortly after leaving this laboratory, to take up the study of the structure of the lung and it has been my life-work since that time. At first, my results apparently confirmed Delafield's statement that the "air-passages seem to be made up of a succession of large vesicles opening into each other." J. West Roosevelt came to his assistance, and showed that if a complete corrosion of the lung be picked to pieces, under a dissecting microscope, small more or less spheroidal bodies could be isolated, and that these bodies had two or more facets which represented the points at which they communicated with similar bodies. I repeated Roosevelt's method and obtained the same results. For the time being it appeared that Delafield's statement was correct, but reconstruction methods gave very different results.

As one studies the diagrams and descriptions of the older investigators it seems as though they were constantly looking for a single section which was cut through as many subdivisions of an air-passage and its ending as possible (fig. 7). Only one investigator (Waters) could visualize more than one air-sac (we will drop the term *infundibulum*) as being connected with a terminal division of the bronchial tree.

When the diagram of Waters is carefully studied there can be recognized, in its centre, a place where three air-sacs join before entering the dilated extremity of the terminal bronchial tube (fig. 3, *c*, *c*, *e*); two of them are represented in their full length while one of them is represented as being cut off. A somewhat similar condition can be seen at their right where two air-sacs join.

Serial sections and reconstruction methods had not been used, or thought of, at that time; and Waters failed to realize that this union of air-sacs and the accompanying external markings suggested a special cavity interposed between the air-sacs and terminal bronchial tube. As soon as reconstruction methods were applied to the study of the architecture of the lung this cavity became an actuality.

If a reconstruction be made of the air-spaces connected with the last division of the bronchial tree, it matters not whether it be from a cat, dog or man, if this reconstruction be cut along a line which continues the long axis of the *ductulus alveolaris* the diagram shown in figure 6 will be obtained.

In this diagram a *bronchiolus respiratorius*, of Kölliker, is seen to divide into two *ductuli alveolares* (*Alveolargänge*) of Schulze. Only one *ductulus* is carried out in full detail. Opening out from this latter by nearly circular openings are three *atria* (fig. 6, *a*, *a*, *a*,). Each atrium is interposed between a group of *sacculi alveolares* (air-sacs) and the expanded end of the *ductulus alveolaris*, while small evaginations of the walls of the *sacculi* form the *alveoli pulmonis*. Alveoli are also present along the *bronchiolus respiratorius*, the *ductuli alveolaris* and the atria. The elongated air-sacs of Waters have now been divided into two parts, namely, atrium and air-sacs.

If the diagram of Waters be again studied, the opening leading out from the expanded end of his terminal bronchial tube, which he describes as opening into an air-sac (fig. 3, *e*) may be interpreted as leading into an atrium and not into an air-sac. It was isolated atria that both Roosevelt and myself obtained when wax corrosions of the lung were picked apart. They are the only portions of a corrosion of the normal air-spaces that show more than one facet.

In the preceding schemes of the ultimate arrangement of the air-spaces within the lung, the lobule, no matter how constituted, has a more or less triangular outline; and the bronchial tube, no matter how named, enters at its apex, with the air-sacs continuing in the general direction of the bronchial tube.

In figure 6 the same triangular outline appears as in the previous figures, but the *ductulus alveolaris* does not join the apex of the triangle: it enters at one side. This point of entrance and the presence of atria allow a greater range of direction to the air-sacs, and some of them, instead of continuing the direction of the *ductulus* toward the periphery of the lobule, have a course in the opposite direction and come to be situated close to the *ductulus* with which they are connected. Because of their direction they may be called *recurrent air-sacs* and they often form the apex of the triangle.

In order that the relation of the various air-spaces shown in figure 6 may be better understood, and to demonstrate more clearly the relations of atria, photomicrographs of sections which entered into a reconstruction of the air-spaces of the human lung were made and reproduced as line drawings.

In figure 8, a^1, an opening is seen marked out by heavy outlines. This leads into an atrium that is situated above the level of the section (compare fig. 3, *e*). Following the air-spaces toward the lower left corner of the section, a chain of small air-spaces (alveoli) can be recognized. These are sections of alveoli which open into the underlying *ductulus alveolaris* and *bronchiolus respiratorius*. The heavy outlines on the left side of the section mark out the walls of a *bronchiolus respiratorius* that belongs to another system of air-spaces.

Figure 9 is a section taken 160 micra below figure 8, and shows not only the *ductulus* with which atrium a^1 communicates, but also a portion of the *bronchiolus respiratorius* from which the *ductulus* arises. Only a reconstruction from serial sections will bring out a differentiation of this nature. Around the distal end of the *ductulus* four air-spaces (a^2, a^2, a^3, a^3) are indicated. These belong to two atria, with corresponding numbers, which are connected with the *ductulus* at a lower level.

Figure 10 is a section taken 240 micra below figure 9, and shows the *bronchiolus respiratorius* cut lengthwise and the two *ductuli alveolares* into which it divides. The openings by which atrium a^2 and atrium a^3 communicate with the *ductulus* appear in this section. Two air-sacs (*sacculi alveolares*) open out of atrium a^3, but none of the air-sacs belonging to atrium a^2 is connected with it in this section.

Figure 11 is a section taken 160 micra below figure 10. The opening by which atrium a^2 communicates with an air-sac is cut through, and a small portion of the opening by which the atrium communicates with its *ductulus* is shown. Three air cells (a^3, a^3, a^3) which belong to the atrium

bearing the same number are seen just at the left of atrium a^2. Only a small portion of the *ductulus alveolaris* which we have been considering remains, while the *ductulus* which first appears in figure 10 is shown cut through its entire length; also a small portion of an atrium and air-sac which are directly continuous with its axis. A very interesting series of air-spaces is seen on the left side of the section, and they furnish a good example of the necessity of serial sections in studying the architecture of the lung. These spaces belong to a still different system and are continuations of the *bronchiolus respiratorius* of which a small portion appears on the extreme left of the section.

The four sections which have been described and analyzed form a block which is 0.5 mm. long, 0.36 mm. wide and 0.6 mm. thick in its greatest measurements. In this block three *bronchioli respiratorii* and their subdivisions have appeared, one of which has been followed out to its ultimate ending in *ductuli alveolares*, atria, *sacculi alveolares*, and alveoli. Certain factors which still further aid in distinguishing the atria will be discussed in the following section.

The *tunica muscularis* of the trachea, which is made up of bands of smooth muscle, is continued into the bronchi where it is often called the *Muscle of Reisseisen*. As the cartilaginous plates disappear from the walls of the bronchi the muscle increases in quantity. In the larger bronchi the muscle is arranged in the form of anastomosing bands, which have a direction nearly transverse to the long axis of the bronchus, but nowhere do they form a complete sheet of muscle as, for example, in the walls of the small intestine. As the *bronchioli respiratorii* are approached the muscle bands take a more oblique course and have a wide, open mesh. This change of direction has an important significance.

In the preceding section it was seen that alveoli were present along the *bronchioli respiratorii* and that the same was true in regard to the *ductuli alveolares*. The openings leading into these alveoli are always situated in the open mesh of the smooth muscle; they could not be otherwise situated. It was also seen that both of these subdivisions of the bronchial tree take part in respiration. This necessitates the providing for a certain amount of movement.

The bronchi and bronchioli do not open and close along the main-stem bronchus like a fan, neither is their movement like that of a bellows. The latter consists of a widening of the angle at which the branches leave the main-stem bronchus; at the same time they become elongated

and narrowed, and a slight rotation takes place. This movement is most marked in the lower lobes, where the amount of movement is the greatest, due to the expansion of the inferior aperture of the thorax and the descent of the diaphragm. It is to accommodate these movements that the change in the muscular network takes place; the muscle now takes the form of geodesic bands which prevent any tangential motion. In this way provision is made for the greatest amount of strength and at the same time permitting the greatest amount of extension and contraction (fig. 12).

Smooth muscle does not extend beyond the ductuli alveolares. Nearly every investigator, who has studied the subject, has confirmed the statement, made by both Kölliker and Schulze, that no muscle is found beyond what is now termed a *ductulus alveolaris*. If sections which apparently show muscle in the walls of the air-spaces be followed through a series of sections it will be found that the muscle does not belong to the air-spaces, but to some division of the bronchial tree or to a blood-vessel.

At the distal end of the *ductuli alveolares* the muscle is arranged in the form of a sphincter about the openings leading into the atria. This arrangement of the muscle about the atrial openings plays an important rôle in many cases of asthma by becoming strongly contracted during the asthmatic attack. Moreover, in the lungs of chronic asthmatic individuals the muscle bands throughout the lung are much thickened. In figure 13, which is a camera lucida tracing of a section through a primary lobule near the distal end of a *ductulus alveolaris*, the position of these bands about the atrial openings are shown; in some places the bands are cut transversely; in other places they are cut lengthwise, depending on the position of the opening leading into the atrium.

That elastic fibres run lengthwise along the bronchial tubes is an old and well-established fact. Some of the early investigators mistook these fibres for muscle, and described an inner longitudinal and an outer circular layer of muscle. These fibres give additional support to the walls of the bronchial tubes, especially where the muscle is deficient; they also take part in the extension and contraction of the bronchi and bronchioli during respiration. With the appearance of alveoli along the walls of a bronchiolus the elastic fibres no longer form a distinct layer, but are continued into the network of elastic fibres which are present in the walls of the air spaces.

The normal lung contains *reticulum*. This is distributed throughout all portions of its framework. In the walls of the alveoli it encloses

within its mesh the capillaries and forms the basement-membrane on which the pulmonary epithelium rests. It is especially abundant in the masses of lymphoid tissue that are situated in the angle formed by dividing bronchi, and in other situations where lymphoid tissue normally occurs.

Associated with the development of a tubercle there is an increased development of reticulum. Previous to the formation of giant cells but few fibrils are present; the giant cells, however, take no part in the formation of reticulum. Within a tubercle the reticulum forms a system of branching and anastomosing fibres which are everywhere present, and enclose within its mesh the giant cells, the endothelial cells and the lymphocytes (fig. 14). This network of fibres is finer in the centre of the tubercle than at its periphery, where they show a tendency to be converted into collagenous fibres. In case the growth of the tubercle becomes arrested this actually occurs, and the tubercle is converted into a dense nodule of collagenous tissue.

There are, however, formations made up originally of single tubercles which have developed separately, but close to each other, which, by their fusion have formed larger or smaller masses called conglomerate tubercles. With the coalescence of the single tubercles to form a conglomerate tubercle certain changes take place. It is no longer spherical in outline but is irregularly oval and lobulated. Its centre soon changes its character; the cells become necrosed and caseation gradually takes place. These changes often occur in the individual tubercles before fusion takes place.

If a section through a conglomerate tubercle, which has undergone caseation in its centre, be stained with haematoxylin and eosin, the caseation appears as a fine granular mass. The special stain for reticulum, however, shows that the caseated area is everywhere invaded with a network of fibrils, that is, the reticulum (fig. 15).

Anatomically three types of tuberculous bronchopneumonia can be recognized. Each type presents a characteristic picture when stained for reticulum.

In type 1 the walls of the alveoli are recognized with difficulty, and there is no increase of reticulum in their walls. No reticulum is found within the alveoli themselves. The exudate which fills the alveoli undergoes an early and rapid caseation. Miliary tubercles are rarely present (fig. 16).

In type 2 the walls of the alveoli are increased in thickness and they

contain an increased amount of reticulum. The alveoli are filled with an exudate in which caseation takes place quite early. Miliary tubercles are present in considerable numbers. The reticulum shows a tendency to encapsulate the caseous areas without, however, extending into the alveoli themselves (fig. 17).

In type 3 the walls of the alveoli are thickened; the alveoli themselves contain an exudate that consists largely of endothelial cells, lymphocytes, and a few polymorphonuclear leucocytes, which are enclosed within a dense network of reticulum. The reticulum in the walls of the alveoli is increased in quantity and is directly continuous with the network within the alveoli. Because of these characteristics which differentiate this type from the two preceding types, I have designated it *reticular pneumonic tuberculosis*. The exudate in other types of pneumonia usually contains threads of fibrin, *never reticulum*. A small amount of fibrin may be present in this type also; but it is reticulum that predominates (fig. 18). Miliary tubercles are present throughout the lung.

A rapidly progressive caseous tuberculosis, apparently the result of an overwhelming infection, is often called "acute phthisis," "phthisis florida," "galloping consumption," and other names too numerous to mention. This may involve a single lobe, the lobar form; or it may occur in a widely disseminated bronchopneumonic form. Both are characterized by a cellular exudate that fills the bronchi and alveoli, and rapidly undergoes caseous necrosis. The bronchopneumonic form is more frequent than the lobar, and corresponds to type 1, described above.

In the lobar form a single lobe may be affected or, rarely, nearly the whole of one lung. The affected lobe presents a complete consolidation. The cut surface may be smooth, or it may be finely granular. The outlines of the alveoli are recognized with difficulty. No tubercles are present and, except in the inflamed and thickened pleura, and the connective-tissue septa, there is no increase of reticulum. The onset of the infection has been too precipitate, and the extension too rapid, for the lung to show any signs of resistance. If the individual live long enough, the caseous mass may break down and extensive cavities be formed.

Reticulum plays an important rôle in pulmonary tuberculosis. If the infection is not a severe one it is constantly trying to wall off infected areas by its conversion into collagenous fibres. Evidence of this is frequently found in miliary tubercles and in the walls of cavities. On the other hand in the bronchopneumonic and lobar forms of caseous

tuberculous pneumonia, in which the lung has been overwhelmed by the invasion of tubercle bacilli, reticulum is but slightly developed.

That reticulum is very resistant is shown by its persistence not only in purely tuberculous processes, but also in those cases in which pulmonary gangrene occurs as a concomitant of tuberculosis. In each instance it is fully as resistant as the elastic fibres.

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EXPLANATION OF FIGURES

FIG. 1. Rossignol's diagram of the lung, 1846. *a:* two adjoining infundibula which have become fused; *b:* the next to the last bronchial division; *c:* a single infundibulum connected with a bronchial tube. Apparently the last division of the bronchial tree since *b* is next to the last division.

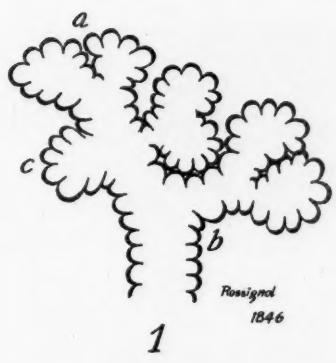
FIG. 2. Kölliker's diagram of the lung, 1852. *a, a:* two primary lobules (sacculi); *b, b:* air-cells or alveoli; *c, c:* the finest bronchial branches; these also possess air-cells.

FIG. 3. Waters's diagram of the lung, 1860. *a:* terminal bronchial tube; *b:* its dilated extremity; *c, c, c:* individual air-sacs; *e, e:* openings leading into other air-sacs. The six air-sacs converge to a common centre.

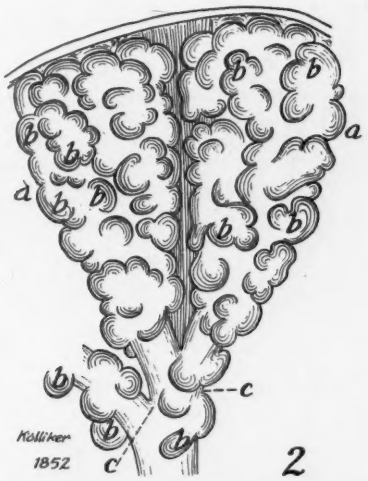
FIG. 4. Schulze's diagram of the lung, 1871. *a:* terminal bronchial branch; *b, b:* infundibula; *c, c:* transverse sections of alveolar passages; *d, d:* longitudinal sections of alveolar passages.

FIG. 5. Kölliker's diagram of the lung, 1881. *br.r.:* bronchiolus respiratorius; *ag, ag.:* two alveolar passages, one of which terminates in an infundibulum. The openings in the walls of these various divisions lead into the alveoli.

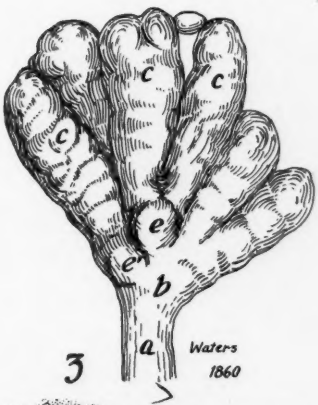
FIG. 6. Author's diagram of the lung slightly modified from his 1892 diagram. *b.r.:* bronchiolus respiratorius; *d. al.:* ductulus alveolaris; *a, a, a:* three atria; *s. al., s. al., s. al.:* sacculi alveolares; *a. p., a. p.:* alveoli pulmonis.


a
c
b
Rossignol
1846

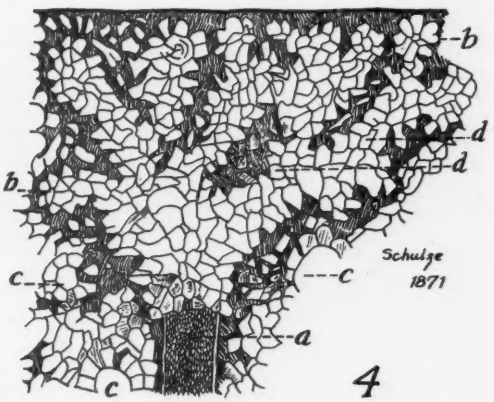
1


a
b
c
Kölliker
1852

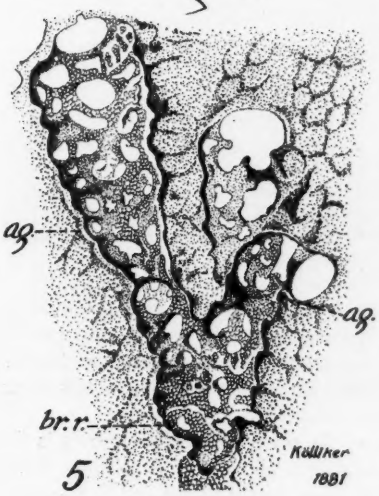
2


c
e
b
a
Waters
1860

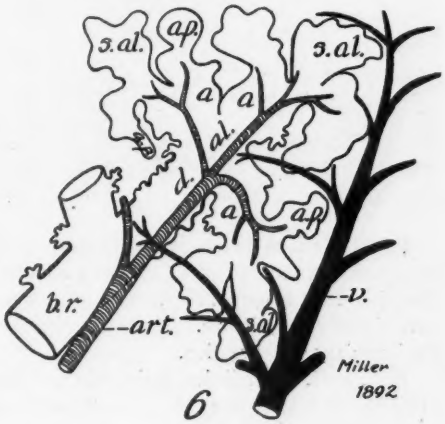
3


b
d
d
b
c
c
a
c
Schulze
1871

4


ag.
ag.
br. r.
Kölliker
1881

5


s.al.
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s.al.
a
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d.
a
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art.
v.
Miller
1892

6

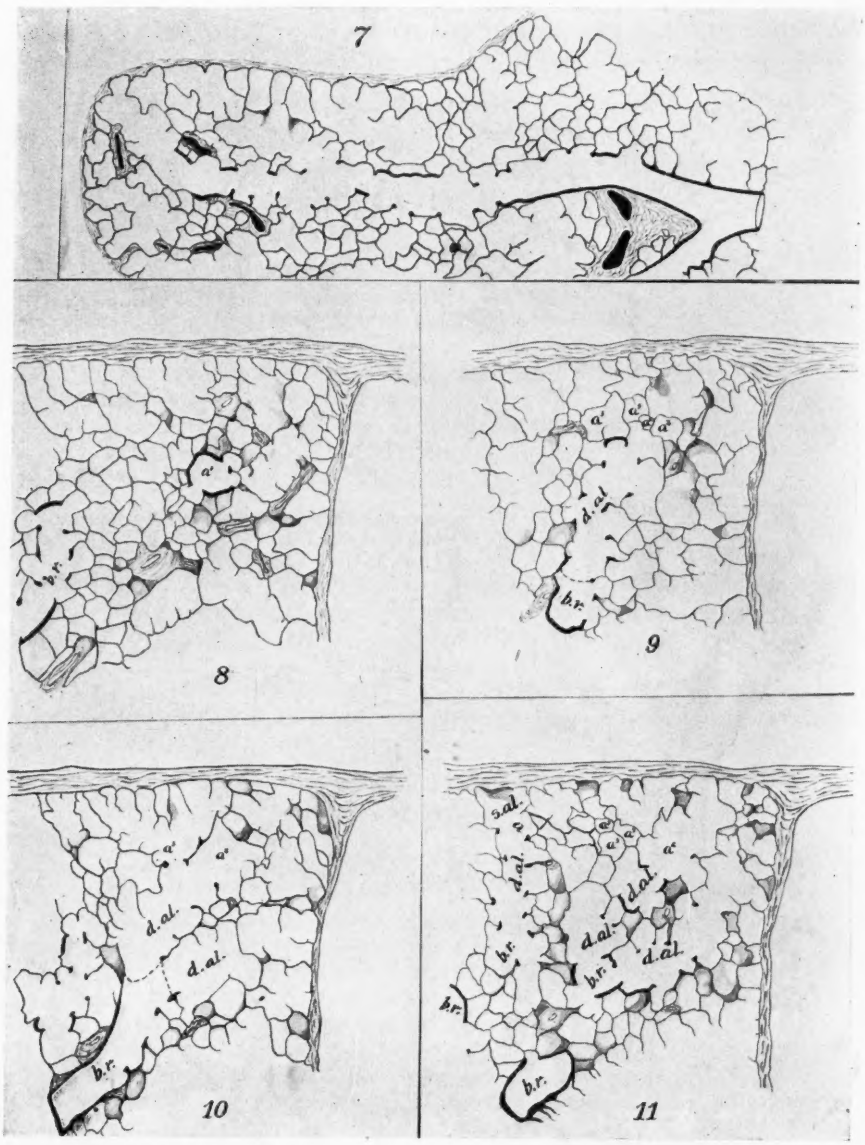

FIG. 7. Camera lucida tracing from a section of a human lung in which a bronchiolus, two bronchioli respiratorii, a ductulus alveolaris, an atrium, and a sacculus alveolaris with its alveoli, are cut longitudinally. This section was taken 6 cm. below the pleura and formed part of a secondary lobule. The connective-tissue septa between the adjoining lobules forms the boundary of the section.

FIGS. 8–11. For full description of these figures see the text. Reference lettering is the same for all four figures. *b. r.*, bronchiolus respiratorius; *a, a, a:* portions of three atria; *s. al.:* sacculus alveolaris. The sections are bounded above by the pleura and on the right by a septum which separates two adjoining secondary lobules from each other.

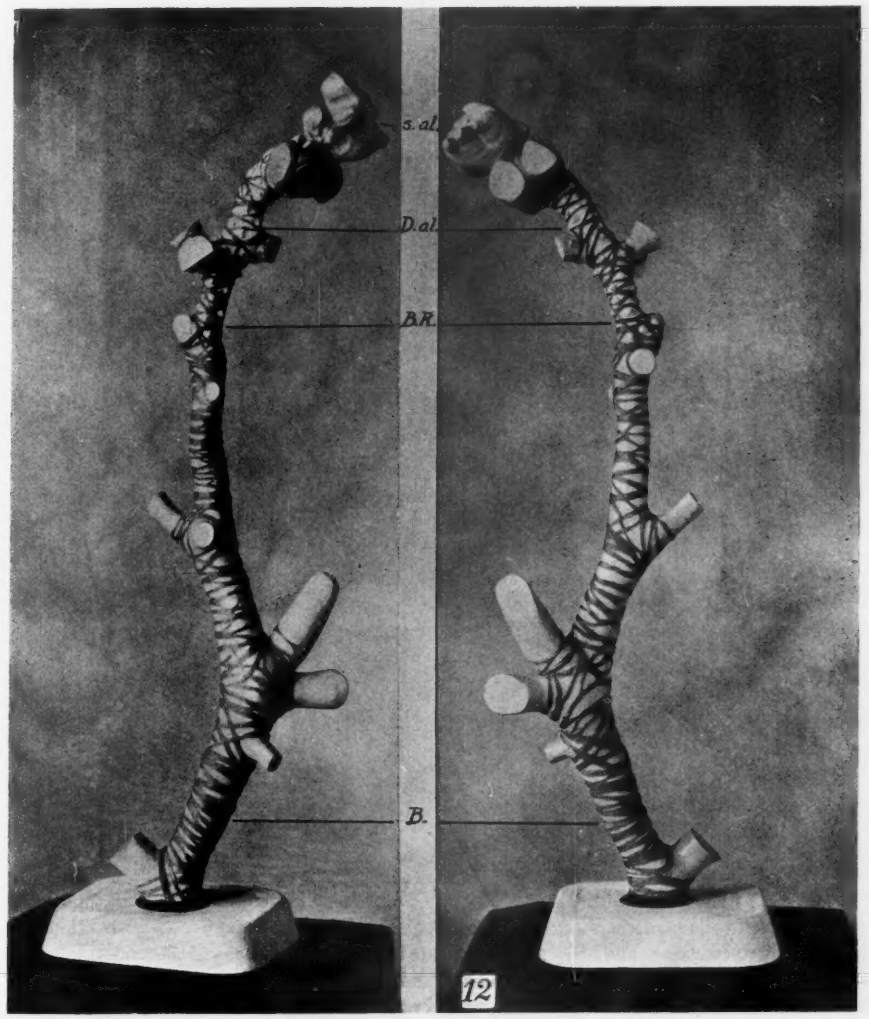

FIG. 12. Two views of a reconstruction showing the distribution of smooth muscle bands. *b.*: bronchiolus; *b. r.*: bronchiolus respiratorius; *d. al.*: ductulus alveolaris; *s. al.*: sacculus alveolaris.

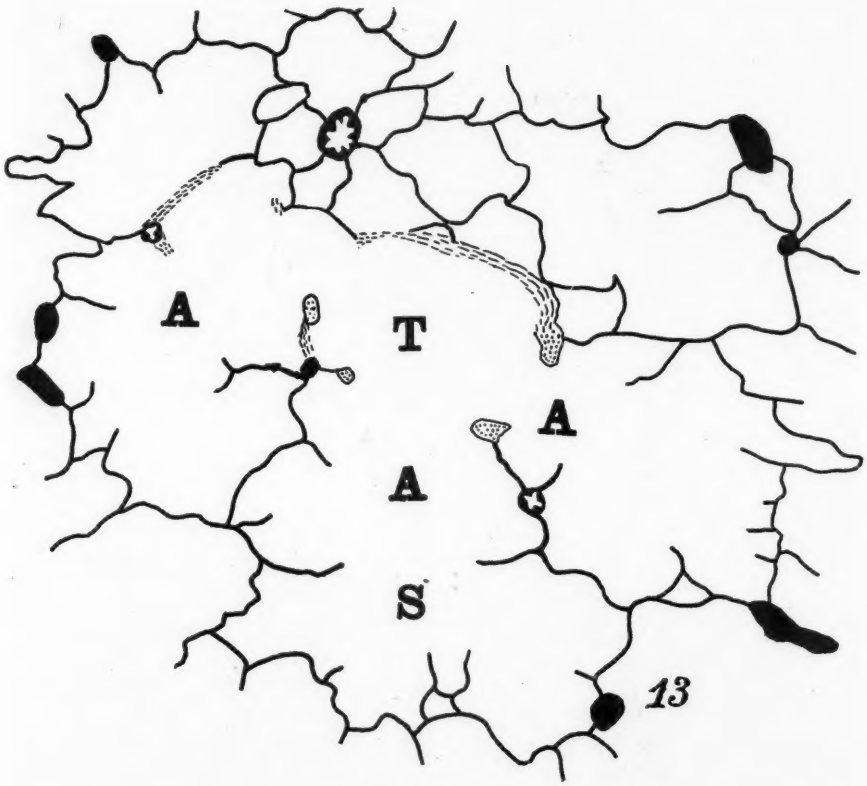

FIG. 13. Camera lucida tracing of a section of a primary lobule taken through the distal end of a ductulus alveolaris. *T.:* ductulus alveolaris; *A, A, A.:* three atria; *S.:* portions of two sacculi alveolares. The broken lines indicate longitudinal sections of the smooth muscle in the walls of the ductulus. The stippled areas indicate transverse sections of the smooth muscle bands about the openings leading into the atria. The pulmonary veins are shown in solid black. The pulmonary arteries have stellate openings in them.

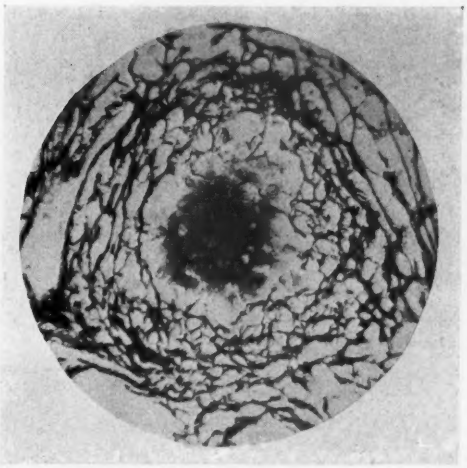

FIG. 14. A single microscopic tubercle enclosed within a basket network of reticulum. Reproduced from the Amer. Rev. Tuberc., 1923, vii, 147.

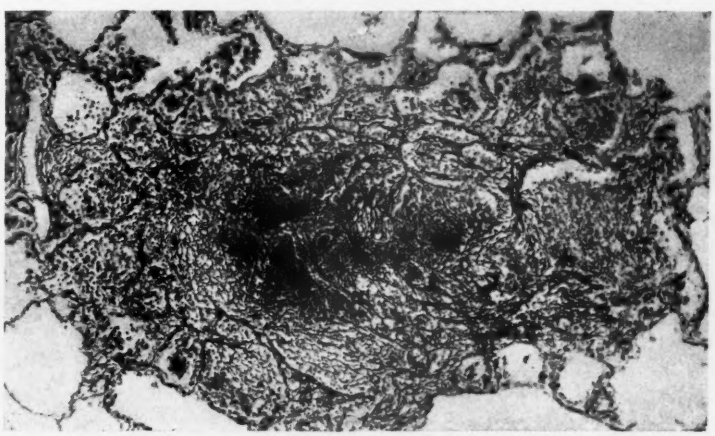

FIG. 15. A conglomerate tubercle, which has undergone caseation in its centre, showing the persistence of reticulum within the caseous centre. Reproduced from the Amer. Rev. Tuberc., 1923, vii, 147.

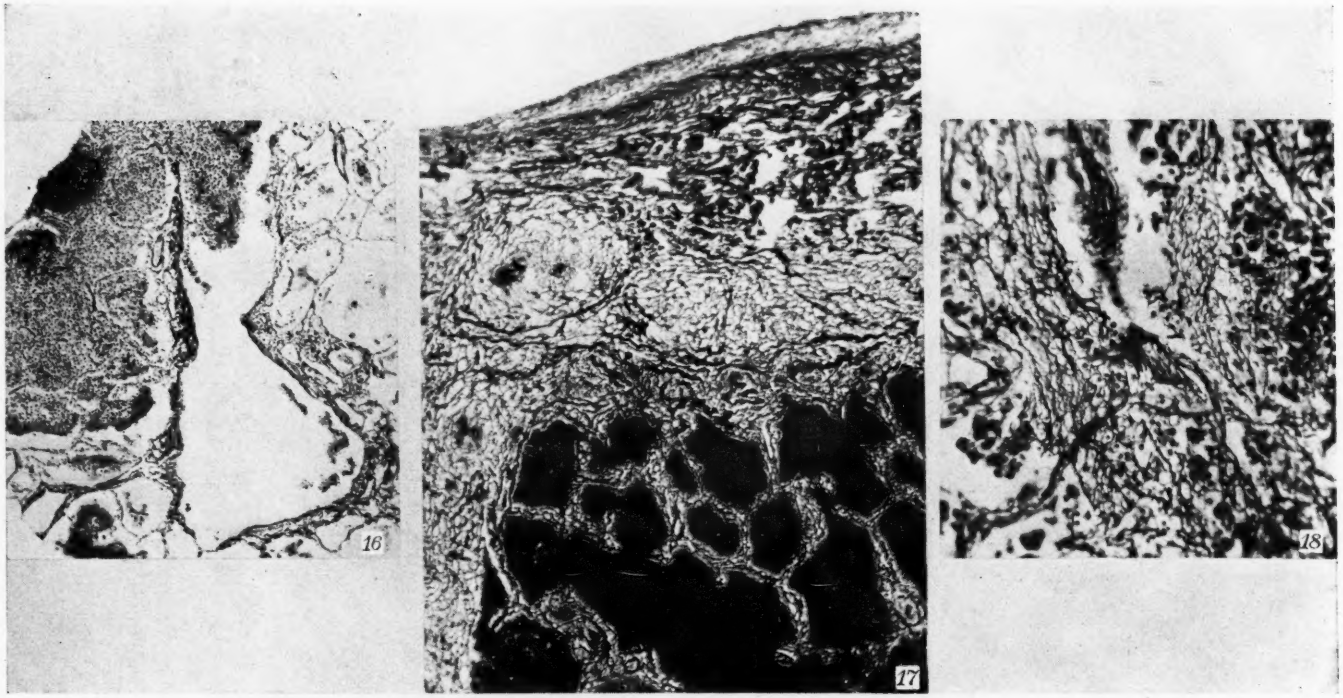

FIG. 16. Type 1 of tuberculous bronchopneumonia. See text. Note the indistinctness of the alveolar walls within the caseous area, that there is no increase of reticulum in the pulmonary framework, and that there is no reticulum within the alveoli.

FIG. 17. Type 2 of tuberculous bronchopneumonia. See text. Note the increased thickness and the increased amount of reticulum in the walls of the alveoli, the great amount of reticulum and of collagenous fibres which form the capsule about the pneumonic area, the absence of reticulum within the alveoli, and the presence of tubercles with giant cells. The upper boundary of the section is formed by a pulmonary vein, and the heavy band of collagenous fibres form part of its wall.

FIG. 18. Type 3 of tuberculous bronchopneumonia. See text. Note the thickened alveolar walls in the lower left quadrant, the great increase of reticulum in their walls and the extension of the reticulum into the lumen of the alveoli.

A REPORT OF RESULTS WITH EXTRAPLEURAL THORACOPLASTY FOR PULMONARY TUBERCULOSIS [1,2]

WILLIAM H. THEARLE[3]

Modern surgical efforts to alter mechanically the course of unilateral, or chiefly unilateral, pulmonary tuberculosis have been developed through experiences gained from pneumothorax therapy during the past twenty years. All are based on the attainment of physiological rest of the diseased lobe or lung by various compression procedures.

The operation at present most frequently performed with any definite results is extrapleural thoracoplasty, which has been developed and standardized by the extensive theoretical and practical work of Sauerbruch. This consists in a subperiosteal resection, posteriorly and close to the vertebral articulations, of various lengths of the 1st or 2nd to the 10th or 11th ribs, in one or more stages. The anterior ends of the ribs drop downward and inward, while a downward shift of the whole chest-wall of one or two interspaces occurs with section of the upper two ribs, especially the first. The flexibility of the cartilaginous extremities of the ribs permits approximation of the resected ends by adhesive strapping of this half of the thorax, which is maintained until they are united by fibrous tissue.

The chest is thus diminished in both diameters, but maintains considerable of its symmetry, although some deformity is inevitable with an extensive resection; the degree of lung compression with resulting rest is directly proportional to the extent and number of ribs removed.

Thoracoplasty belongs to the same category in the treatment of pulmonary tuberculosis as artificial pneumothorax, and the indications for its performance coincide generally with those for pneumothorax, namely, progressive unilateral phthisis with a slight (preferably arrested) lesion in the other lung, which is competent to carry on the added respiratory

[1] Read before the Sanatorium Societies of Denver and El Paso Counties, at their seventh joint meeting, June 28, 1924.

[2] Published with the permission of the Surgeon-General, U. S. Army.

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function without activation or extension of lesions, and after pneumothorax has been tried without success or is impracticable because of pleural adhesions.

Among the *contraindications* are (1) amyloid visceral disease, (2) extensive lesions in the better lung, (3) miliary tuberculosis, (4) tuberculous peritonitis, and (5) any serious disease elsewhere in the body, especially nephritis.

Thoracoplasty is not advocated to replace the simpler and safer procedure of artificial pneumothorax, which should invariably be tried first, and proved not feasible before more radical operative measures are resorted to. Surgical collapse must be considered a more serious procedure with a necessarily more limited field of applicability than pneumothorax, for the following reasons:

1. It is associated with some degree of shock, that is directly dependent on the physical condition of the individual, and is thus a strain on resistance and recovery in any case of tuberculosis.

2. The lung collapse, instead of being a gradual accomplishment as in pneumothorax, occurs immediately, with the result that there are more mechanical and toxic disturbances, and more risk of aspiration pneumonia or tuberculosis in the other lung or in uncollapsed portions of the bad lung.

3. The collapse is permanent and not remediable as is the case in artificial pneumothorax in which the lung can often be allowed to reexpand to some degree if trouble threatens or develops in the better lung.

The advantage of thoracoplasty over gas compression is the immediate definite collapse, which makes unnecessary the usually long period of medical surveillance, with its many and frequent refills, in pneumothorax therapy; a period which in time is not uncommonly associated with serous or purulent pleural exudates, as well as the danger of rupture of the lung and its very high mortality.

Surgically, any degree of collapse can be obtained that is accomplished by air therapy, but this must be planned in advance according to the indications present and the extent of pulmonary rest considered necessary in the individual case.

The cases particularly suitable for operation are the "chronics," whose lungs show fibrosis with cavitation, but in whom Nature is powerless to effect eventual healing because such cavities are held open by fibrous pulmonary and pleural adhesions to a rigid chest-wall. In such cases, because of adhesions, attempts at pneumothorax are only

partially successful, and usually impossible. The prognosis is poor, and often hopeless, in spite of the best expectant sanatorium treatment, and the patients gradually lose ground, as they experience febrile exacerbations, not infrequently pulmonary hemorrhages, aspiration extensions and degenerative visceral changes, especially amyloidosis, from prolonged mild toxemia.

Our limited experience with thoracoplasty has firmly convinced us of the importance of operation at an earlier stage of the disease than has been customary, and that it should be advised without delay as soon as sufficient observation has demonstrated an apparently hopeless outlook under ordinary conservative treatment and when pneumothorax is rendered impossible by adhesions.

A one-stage operation is generally considered preferable to a two-stage procedure when practicable; resection is performed from below upward to minimize the risks of aspiration especially,—also hemorrhage and later bronchiectasis,—in the lower lobes, that obtain when the upper portion of the lung is first collapsed.

The critical period in these cases, especially in a single-stage collapse, is usually the first few days after operation, and a favorable result depends on the patient's recuperative powers and close attention to details, prompt symptomatic treatment and careful nursing. The primary danger is cardiac failure, consequent to too extensive removal of ribs and the resulting changed thoracic relations, which further embarrass a heart always weakened by absorption from pulmonary cavities in proportion to their duration. A little later there occurs the danger of aspiration and pneumonia, while remotely, weeks or months afterward, is the ever possible tuberculous aggravation in the better lung.

Results: During a period of 20 months thoracoplastic collapse has been done by us on 25 patients, 9 of whom had an associated pneumothorax. The chief involvement was in the left lung in 14. A one-stage collapse was performed on 10 patients.

A case is not classified as a practical cure until at least two years have passed since operation, which period has not elapsed in the cases of this series. Of our patients the disease was apparently arrested in 7 cases, and improved in 9, while 5 have died.

Sauerbruch reports 35 per cent as cured, 40 per cent definitely improved, and a 12 per cent mortality (437 cases). Bull, in a recent article, reports 82 extrapleural thoracoplasties observed from one to nine years after operation, with 32 deaths, a mortality of 39 per cent;

9 died from operation, 22 from tuberculosis, and one from other causes. Of 73 surviving the operation, 35 are free from symptoms, while 15 are now tuberculous, but 9 of these have been benefited.

Brief histories of 8 completed cases with roentgenographic studies and the presentation of 7 patients will illustrate the results obtained by thoracoplasty in our cases. All patients underwent operation under local analgesia, except one "neurotic" who required the addition of nitrous-oxide anesthesia.

Case 1: Female, age 27. Tuberculosis developed in France in 1918. Has been in various institutions, mostly as bed patient since, but condition has gradually become worse. Frequent distressing cough, with three-quarters of a cup sputum daily, weakness, dyspnea, and frequently little evening rise of temperature. One-stage left thoracoplasty, 2nd to 11th ribs (4 to 6 inch resection). *Lungs:* Tuberculosis, chronic, active, both lobes left, with multiple cavitation; slight activity right upper, inactive right lower. Operation, September 28, 1923. Convalescence stormy first week, rapid pulse (130). Dyspnea, with some cyanosis from extensive right pleural adhesions; impaired kidney function. Now ambulatory, no cough or sputum. Disease apparently arrested.

Case 2: Male, age 32, five years tuberculosis, bed patient last 15 months, syphilitic. Urine on several examinations showed trace albumin, but blood chemistry and functional tests normal. Slight laryngitis. Sputum about half-cup daily, morning cough chiefly. Condition fair; prognosis poor. Lungs showed activity all lobes right, with extensive cavitation; slight scattered activity both lobes left, with a small cavity upper lobe. November 23, 1923: one stage thoracoplasty, 3 to 5 inch resection 2nd to 11th ribs. Hematoma in wound which became infected. After union of rib ends, respiratory movement of chest restricted by belt because of cavity on left side. Condition decidedly improved. Slight morning cough and sputum, negative for tubercle bacilli past month. Semi-ambulatory. Urine shows trace of albumin with few casts. Plastic operation on scar, June 3, 1924.

Case 3: Male, age 35, was in action in France and slightly gassed in 1918. Operation for left popliteal phlebitis 5 years ago. Tuberculosis diagnosed autumn of 1922, but had cough, with much weakness and loss of strength, for several months previously. Disease slowly extending. February 11, 1924, a one-stage right extrapleural thoracoplasty was performed (4 to 6 inch resection of 2nd to 11th ribs). *Condition of lungs:* Activity all lobes right, with cavity one-half inch diameter upper lobe; inactive lesions left lobes. *Complication:* Simple phlebitis of right median basilic vein appeared one week after intravenous saline infusion. Two weeks later right femoral and then left femoral vein became similarly affected, which confined him to bed much longer than ordinary case and has retarded his convalescence. Is now ambulatory, with slight morning cough and expectoration, and is progressively improving.

Case 4: Male, age 30, five years tuberculosis, with uninterrupted hospitalization. Ambulatory during greater part of this period. Progressive downward course with moderate nocturnal cough and half-cup sputum daily. *Lung involvement:* Active lesions both lobes left, with large cavity in upper lobe; inactivity right upper. Three-stage thoracoplasty November 3 and December 15, 1922, and April 15, 1924. First rib divided, 3 inches of 2nd, and 4 inches of 3rd to 11th ribs resected. Patient now has scant cough and morning expectoration, and has shown marked improvement.

Case 5: Male, age 34, developed tuberculosis while on field service in Mexico, 1916. Improved in 18 months, when he tried to do office work, but symptoms recurred with increased

severity, and he has been hospitalized for past 6 years. Tuberculous arthritis left ankle, 1921. Pulmonary lesions gradually extended. Tired quite easily, dyspnea on exertion, 20 pounds under weight. Two-stage thoracoplasty performed from above downward, 3 to 5 inches of 1st to 10th ribs resected July, 1923, and March, 1924. *Lungs at operation:* Activity all lobes right, with large cavity upper lobe; inactive left upper. Extensive pleural adhesions both lungs. Sputum a cup daily. Moderate improvement after first stage but this has been marked for past 3 months. No sputum or cough at present, and disease apparently arrested.

Case 6: Male, age 27, tuberculosis the sequel to influenza in 1918. Little cough, several hemorrhages May, 1919, when he was first hospitalized, with activity left upper lobe. Improved, and discharged September, 1920, when he took up study of law. Got along well till November, 1923, when he began running fever, slight cough, general malaise, and ached all over. Rehospitalized for pulmonary tuberculosis, chronic, active, all lobes right (upper slight); cavity apex right lower lobe opposite 7th and 8th ribs, with aspiration tuberculosis. Bronchopneumonia below cavity. Eight attempts at pneumothorax unsuccessful; cavity with lesions in right lower lobe increasing. General condition good. March 7, 1924, 3.5 inches of 4th to 10th ribs resected posteriorly. Convalescence uneventful except for some rapidity of pulse first week. No cough or expectoration now, cavity obliterated, lesions apparently arrested.

Case 7: Male, age 33, 4 years tuberculosis with left pyopneumothorax. Bed patient most of time, progressively losing ground. Physical condition poor, fever and sweats, frequent cough, particularly at night, loss of weight and strength, marked dyspnea on exertion. Some edema of feet and legs. Two cups sputum daily. Tuberculosis of left ankle. *Lungs:* Active lesions all lobes left and upper lobe right; inactive lower and middle right lobes; small cavity left upper; fluid level left pleura to 4th rib. Two-stage left thoracoplasty July and December, 1923. Four to 5 inches of 2nd to 11th ribs resected; patient's condition did not warrant resection 1st rib as intended in 2nd stage. Lung reëxpanded, which completed obliteration of left pleural space. Improvement has been marked in this case; considerable gain in weight and strength. No cough or sputum for 5 months. Disease apparently arrested.

Case 8: Male, age 36, 9 years tuberculosis, hospitalized 4 years at Ft. Bayard, and received left artificial pneumothorax 1916 for two years. Improvement rapid and marked. Was on active duty during war. Developed influenza September, 1918, but never completely recovered; lung had reëxpanded and tuberculosis became active again. Night sweats, with fever, increased cough and expectoration; rehospitalized this institution, July, 1921. Pneumothorax tried, but adherent pleura permitted admission of only very small amount of air, and repeated attempts unsuccessful. Patient improved sufficiently, however, to be allowed to return to his home in Denver, April, 1921. One month out of every six he spent in bed because of fever with sweats. January 24, 1924, returned to hospital in poor condition, anemic and quite toxic, with frequent cough and 1 cup sputum daily. Temperature 102 to 103.8°, with drenching sweats, dyspnea. B.P., 115 to 70. *Lungs:* Active lesions all lobes left, with multiple cavitation, and slight scattered activity through right lung, with great deal of fibrosis. Heart pulled to left 1 inch by adhesions. January 18, 1924, one stage extrapleural thoracoplasty, 4 inches of 2nd and 11th, and 6 inches of 3rd to 10th left ribs.

Convalescence uneventful with rapid improvement, except for postoperative shock, which required blood transfusion. Patient has gained 22 pounds, and is now ambulatory, feeling better than he has for years. Cough has disappeared. Left lung is well collapsed and obliteration of cavities has corrected the cardiac displacement and dyspnea. We do not believe that there is any branch of surgery in which the results are more brilliant or striking than thoracoplasty in such a rapidly progressive and hopeless case of pulmonary tuberculosis.

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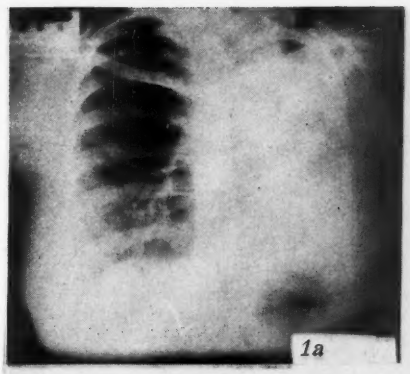
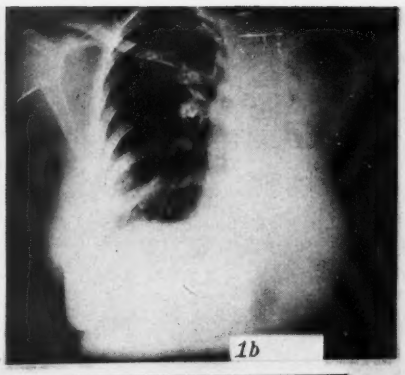
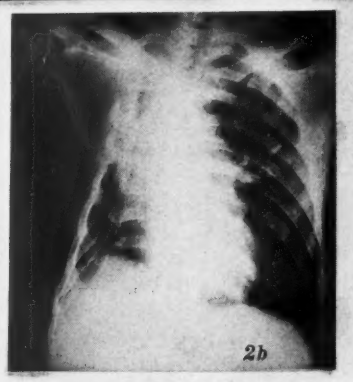
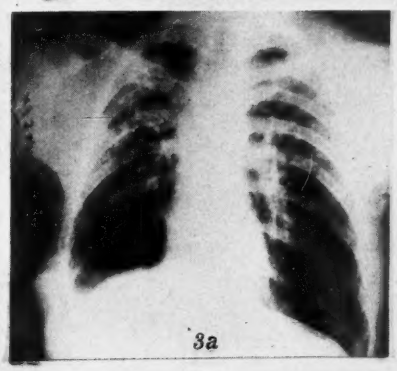
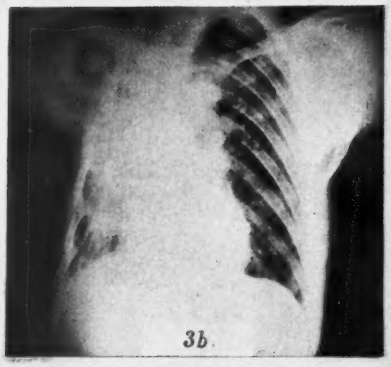
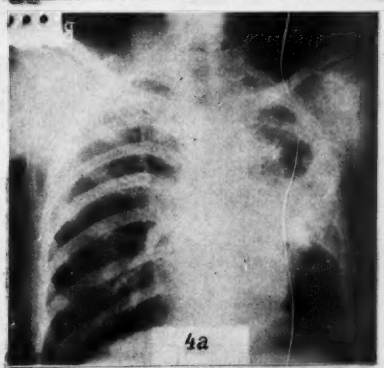


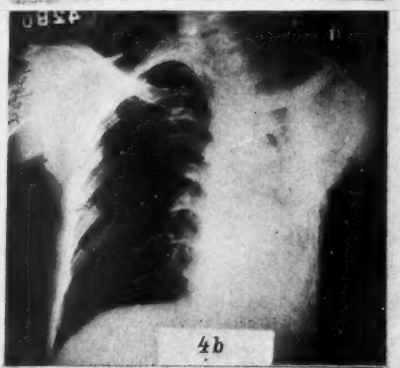




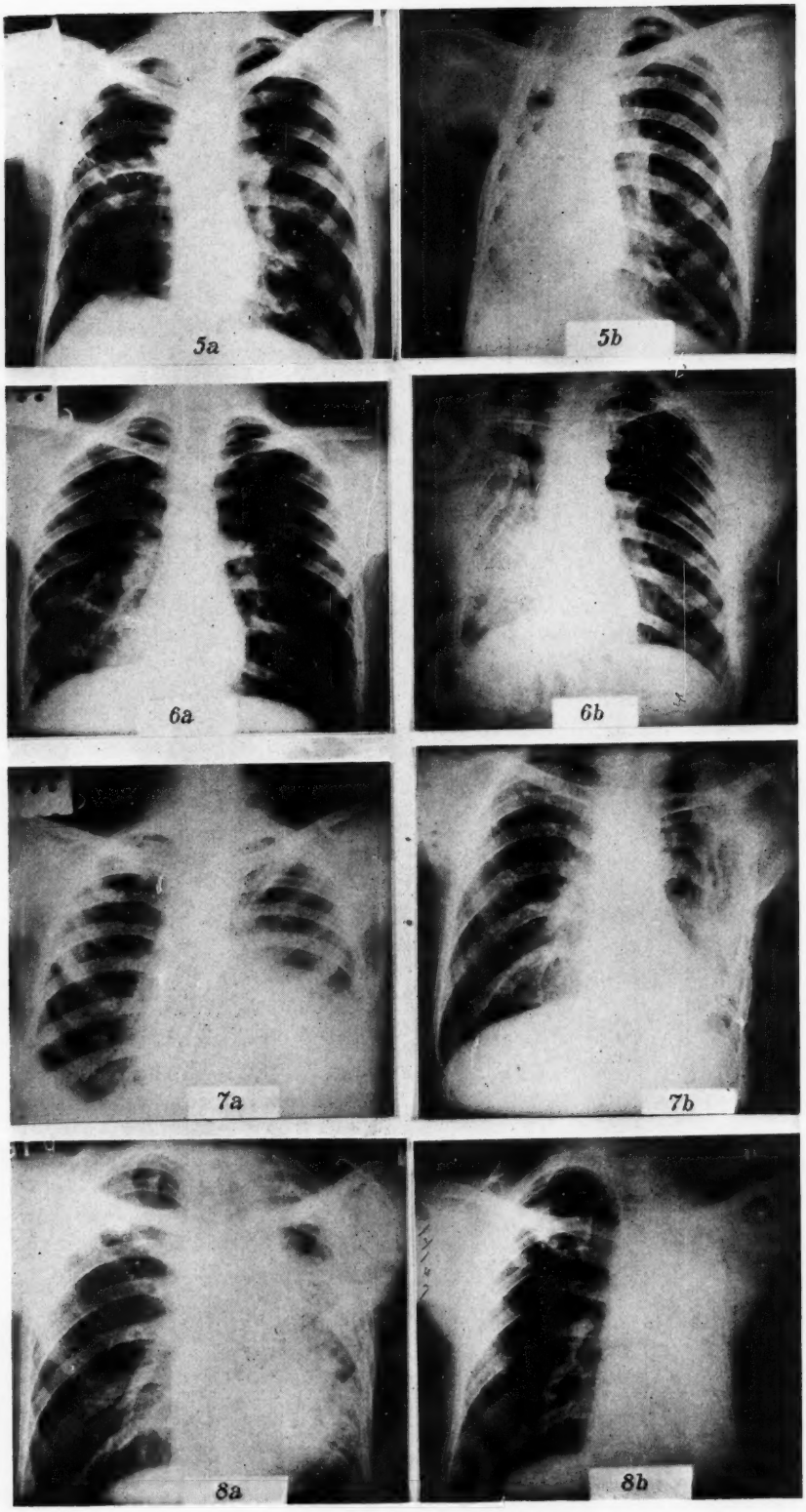








The left-hand figures refer to the corresponding cases before operation, and the right-hand figures to the same cases after operation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LOCALIZED REST IN THE TREATMENT OF PULMONARY TUBERCULOSIS [1,2]

WITH SPECIAL REFERENCE TO EXTRAPLEURAL THORACOPLASTY

ERNEST S. MARIETTE

The treatment of tuberculosis centres about rest of the diseased part. The more complete the rest, the more rapid and sure is recovery likely to be.

There are two distinct types of rest, namely, general and localized rest. Rest in the sanatorium sense means putting the patient to bed. This generalized rest produces only relative freedom from respiratory activity. Since tuberculosis, when given half a chance, is so frequently cured by nature, this amount of rest gives the average patient an adequate opportunity for recovery with the least possible permanent interference with the functional activity of the diseased lung.

Where it is not sufficient some means must be employed to produce localized rest in addition to the general rest. Complete localized rest in pulmonary tuberculosis results in freedom from respiratory activity. This can be partially attained medically by external measures which tend to compress the ribs and lungs. Postural rest, that is, lying on the diseased side for twenty-three and one-half hours a day and the placing of sand-bags on the affected side are methods commonly used for this purpose. More complete localized rest can be attained by surgical means at the expense of the rib-support and diaphragmatic action. Interference with the action of the diaphragm is secured by phrenicotomy which paralyzes the diaphragm and permits its retraction upward into the thoracic cavity, and results in the limitation of movement of the apex as well as of the base. Interference with the rib-support is secured by means of intrathoracic implantation of paraffin, by artificial pneumothorax, or by extrapleural thoracoplasty. All of these surgical methods have the same aim, that is, immobilization and collapse of the

[1] From the Glen Lake Sanatorium, Oak Terrace, Minnesota, and the Department of Medicine, University of Minnesota.

[2] Read before the Clinical Section at the annual meeting of the National Tuberculosis Association, Atlanta, Georgia, May, 1924.

diseased lung, and they result in a more or less complete diminution of respiratory activity; or, in other words, localized rest.

The first method, thoracic implantation of paraffin, is not used extensively in America because of the tendency of the paraffin to exude from the wound.

Essentially the same results are accomplished by pneumothorax as by extrapleural thoracoplasty, although their procedures are radically different. The compression of the lung in pneumothorax is gradual, and produces a slow influx of toxins into the system and a gradual increase in the strain on the good lung. The inconveniences of artificial pneumothorax are the necessity of continuous refills, pleural shock, air embolism, pleural effusion and empyema. At any time, however, should the good lung "go bad," the pneumothorax may be discontinued and the compressed lung allowed to reëxpand, since no permanent interference with the functional activity of the diseased lung has taken place.

Extrapleural thoracoplasty, on the other hand, while producing a collapse in most cases equal to a good partial pneumothorax, does this very rapidly, and results in a sudden flooding of the system with toxins and an abrupt increase in the strain on the good lung. It also allows no possibility of lung reëxpansion if the good lung "goes bad." Its effect is a permanent and irrevocable interference with the functional activity of the compressed lung. Extrapleural thoracoplasty, then, is the most radical measure for bringing about localized rest in the treatment of pulmonary tuberculosis, and should be reserved for those cases in which ordinary sanatorium treatment, including the medical measures for producing localized rest, has not been sufficient, and artificial pneumothorax has been tried and has failed.

Nature, in her attempt to cure certain types of pulmonary tuberculosis, gives man his best argument for extrapleural thoracoplasty, or localized rest. The fibrous tissue, formed in the lung during healing, contracts and causes a shrinkage in the lung, resulting either in a deviation of the mediastinum, an elevation of the diaphragm, or a falling in or depression of the ribs. When the ribs fall in or are depressed we have somewhat the same results that are obtained by extrapleural thoracoplasty, although they are not nearly so complete.

As regards extrapleural thoracoplasty Quincke, in 1888, advocated the removal of the rib overlying a cavity, claiming that it was the rigid, bony thorax which prevented the collapse of the walls of the cavity upon the contraction of the fibrous tissue formed in the lung during healing.

At first, as was to be expected, thoracoplasties were comparatively local, but experience with artificial pneumothorax proved clearly that a complete collapse of the lung gave a much better result than a partial collapse. Accordingly, Bauer in 1907 decided that a large part of the ribs must be removed if results comparable to those of pneumothorax were to be achieved by thoracoplasty. The methods differed widely and were very radical and mutilating, but the technique was gradually modified so that the ribs only were removed. Every one was trying to find a method which would give the maximum collapse of the chest wall and the underlying lung with a minimum degree of danger to the patient's life and his future capacity for work, and so the more simple the operation the better.

Indications: 1. Whenever pneumothorax is indicated but cannot be used because of adhesions. The well lung should be practically free from disease and, of course, the better the general condition of the patient, the better the chance of success. Therefore, one should not wait too long in the presence of high fever and expectoration.

2. A lung honeycombed with cavities is always a source of danger to the patient and it should never be allowed to function again. The choice, then, would lie between pneumothorax, kept up throughout the lifetime of the patient, and extrapleural thoracoplasty.

3. Whenever we have a partial pneumothorax with the base collapsed, and the diseased apex is held out by adhesions. In such cases one can continue the pneumothorax, considering it the first stage, and proceed to operate upon the apex, thus saving the patient the inconvenience of the second operation. This is done with the realization that the pneumothorax will either have to be kept up indefinitely, or that, when it is discontinued and the lung allowed to reëxpand, adhesions may form and a relapse follow, making a thoracoplasty of the base imperative. The physician and surgeon will have to take that risk when deciding to produce only a partial thoracoplasty.

4. Whenever a discontinuance of the pneumothorax and the re-expansion of the lung would result in local areas of fibrosis and emphysema. The emphysematous areas would not increase the aerated tissue of the lung, but would provide a chance for chronic bronchitis, etc. The choice, then, is between thoracoplasty, which will let the bony thorax close in about the lung, or a continuation of pneumothorax throughout the life of the patient.

5. Whenever the economic factor is an important one, and it is necessary to reduce the time of treatment by one, two or several years.

6. Cases of repeated hemoptysis in which pneumothorax cannot be used.

7. Cases in which fibrosis has resulted in a shrinkage of the lung, with marked dislocation of the heart and trachea.

8. The chronic case, with or without cavity formation, which shows some evidence of fibrosis, is the most suitable type for thoracoplasty.

Contraindications: 1. Acute, rapidly spreading caseating cases are bad risks. In spite of this, however, one should not be too hesitant about the use of thoracoplasty when pneumothorax cannot be used. Philip King Brown claims that the wrong, if there is one, lies in leaving the condition to be dealt with surgically as a last resort.

2. Acute flare-ups following the first operation are not necessarily fatal, but the second operation should be postponed until the acute condition has subsided.

3. Active tuberculosis in the good lung. The operated lung can never reëxpand if the good lung flares up. Therefore, one should be more particular about the condition of the good lung in considering thoracoplasty than in considering pneumothorax.

4. Tuberculous complications in other organs of the body, such as kidney, intestines, peritoneum, etc., because they increase the surgical risk, which at best is poor. Much can be done for peritoneal and intestinal tuberculosis with the quartz-mercury-vapor lamp, and the condition of many of these patients will be so markedly improved after its use that they may become suitable cases for extrapleural thoracoplasty. The reduction of toxemia following the operation should have a beneficial effect upon the tuberculous complications, provided the condition of the patient will stand the surgical strain. Slight laryngeal tuberculosis is not a contraindication because the reduction in the cough and expectoration which will follow the operation will have a beneficial effect upon the larynx on account of the increased amount of rest.

5. Chronic bronchitis in the good lung, because of the possibility of this resulting in bronchiectasis or bronchopneumonia following the operation.

6. In addition to the above we have, of course, the contraindications that would hold good for any major operation. After all, the question of extrapleural thoracoplasty is up to the judgment of the physician and the surgeon.

Coöperation: From the indications and contraindications one can readily see that extrapleural thoracoplasty is to be used only after

the medical measures available for the treatment of pulmonary tuberculosis have failed. Therefore, the question of the closest "team work" or coöperation between the physician and the surgeon is of paramount importance.

The physician should know something of the general method of thoracoplasty and the management of the cases, because the treatment of tuberculosis is primarily medical, and the selection of the cases and their after-care will fall largely on him. Whatever surgery is used to compress the lung is not a "cure all" as is an appendicectomy, but is merely an incident in the long medical treatment of tuberculosis; and it should be prescribed and supervised by the medical man as closely as any other therapeutic measure. By the time the physician has decided that thoracoplasty is necessary he should have had time to learn the extent and severity of the pulmonary pathological changes and should then be in a position to advise the surgeon as to the result he desires to attain by means of surgical interference.

Better results can be obtained if the patient can be operated on at a sanatorium rather than in a general hospital, because the tuberculosis patient needs special after-care, which is best understood by the man who is especially trained in tuberculosis.

The Operation: All of the thoracoplasties that have been performed upon the Glen Lake Sanatorium patients have been done at the Sanatorium by Dr. A. A. Law of the Medical School of the University of Minnesota. He has used local anesthesia, combined with gas and oxygen, because, according to him, he does not like to have his "patient present at the operation."

All of the operations have been of the type known as the *posterior*, and all but one in two or more stages. The first intelligent and satisfactory explanation of why the posterior operation gives the best results was given by Boiffin and Gourdet in the middle eighteen-nineties. The explanation quoted from Bull is as follows:

> The rib-cartilage in front is yielding and the anterior part of the rib can be pushed backward and inward, while the posterior portion is stiff and, practically speaking, immovably connected with the vertebral column, and can only slightly be moved up and down. Further, the posterior part of the rib exhibits a marked concavity forward or, in other words, forms an arc, the radius of which is much less than the arc of the ribs otherwise. The angle of the ribs forms a most permanent point of the arc behind. Any section of the rib which is situated in front of the angle of the rib leaves behind a stiff, unyielding piece of the rib which, in accordance with its length, will prevent the soft part from falling in and thus diminishing the costovertebral angle. On the other hand, removal of the stiff posterior part permits the

anterior part to be turned backward toward the spine, so that the arc of the curve of the rib is considerably decreased and the volume of the thorax is correspondingly reduced. Also, the soft parts can move very easily over the yielding anterior ribs, but they are stretched over the stiff projecting end of the rib.

The four figures in diagram 1 are copied from Gourdet:

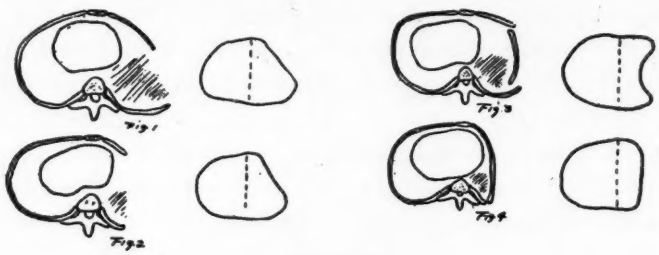

DIAGRAM 1

Figure 1. Results of an Estlander operation upon a cadaver after resection of five ribs. *Effect:* reduction of circumference of chest by 4 cm.

Figure 2. Same operation, but larger resection. Eight ribs removed. Total 110 cm. *Effect:* reduction of circumference by 5.5 cm.

Figure 3. Result of E. Quenu's operation. Resection, before and behind, of a small piece of each of seven ribs. *Effect:* reduction of circumference by 3 cm.

Figure 4. Boiffin-Gourdet operation on a cadaver. Resection of 6 cm. of nine ribs; in all, 54 cm. *Effect:* 8 cm. reduction of circumference. One sees how the front end of the resected ribs can be drawn backward to make contact with the posterior end. The costo-vertebral angle has been almost obliterated.

The posterior operation has been advocated chiefly by Sauerbruch and Saugman in Europe and by Archibald in Canada, and is safer and easier than any other, and is, therefore, the one of choice.

Our experience with pneumothorax has clearly proved that a gradual compression of the diseased lung results in a gradually increased strain on the good lung, and produces far better results than a complete compression of the diseased lung with one inflation. I can see no reason for ignoring this experience, as is so frequently done when the entire side is collapsed at one time by extrapleural thoracoplasty. Really, it seems to me that because the condition is permanent and irrevocable, and because we have to be more particular about the condition of the good lung, we should be even more desirous of producing a gradual collapse. The base from the 11th to the 6th or 5th rib should be operated on first and the remaining ribs afterward. This reduces the danger of aspiration pneumonia which might occur if the process were reversed. We feel that the inconveniences of the second operation are more than

offset by its advantages to the patient. I can see no justification for the one-stage operation except in those rare cases in which the patient refuses to submit to more than one operation. We have never, in our series of 12 cases, had any patient refuse a second operation. The combination of gas and oxygen with the local anesthetic may have been largely responsible for their decision. Occasionally, one finds a surgeon who wishes to take out portions of the central ribs and leave the upper and lower ribs untouched. This produces only a partial thoracoplasty and again ignores our experience with pneumothorax, and means that the patient will have to have three or more operations if the maximum amount of benefit is to be secured from the thoracoplasty.

The extent and severity of the pulmonary tuberculous involvement will determine which ribs, and the amount of each rib, that must be removed in order to produce the desired collapse. The lung will occupy a certain amount of space in the pleural cavity, and our aim should be to have the thorax close in about the shrunken lung. This can be accomplished with a fair degree of success, considering the individual cases, by resection of about 12 cm. of the 10th and 9th ribs and 15 cm. of the 8th to 5th ribs inclusive and 10 cm. of the 4th to 2nd ribs inclusive. The cartilage of the upper ribs is shorter and stiffer than that of the lower ribs, and therefore the anterior segment is not as movable as that of the lower ones. This makes it necessary to remove relatively more of these ribs in order to obtain the desired collapse over the apex. In pronounced disease of the upper lobe, when it is imperative that a good collapse be secured, it will be necessary to resect both the first and second ribs. Even that may not produce the desired results, and then an intrathoracic transplantation of fat, or other substance, may be used to increase the pressure. Some have recommended apicolysis, but the mortality rate from this is very high, and to date we have not used this method.

When there is relatively little disease in the apex, the greater amount being at the base, resection of the ribs up to and including the second will be sufficient. One might question the advisability of removing so many ribs in basal disease were it not for our experience with pneumothorax, which has clearly proved that a complete collapse gives a much better result than a partial one. If the ribs up to the fourth are removed the scapula is held out, and only the angle can fall into the depression. The scapula in its entirety, especially along its posterior edge, cannot fall in until all of the ribs against which it lies are resected.

This was beautifully illustrated in one of our early cases in which the ribs were not removed close enough to the spinal column and the scapula rested against the projecting ribs. After the projecting ends of the ribs were removed the scapula fell in and the compression was a great deal more complete.

The removal of the 11th rib will not materially affect the collapse of the lung, but it will tend to immobilize the diaphragm, and also permit its retraction upward into the thoracic cavity along with the retraction of the fibrous tissue formed in the lung during healing. We are using the procedure in place of phrenicotomy and, of course, the degree of mobility of the diaphragm, whether it is freely movable or bound down by adhesions, will have a marked effect on the result following the removal of the 11th rib.

Postoperative treatment: The bandage should be tight enough to slightly compress the side, and also support it during cough, but still not so tight as to compress the well side and diminish respiration. As soon as the patient can stand it, postural rest should be used to increase the amount of local rest and guide the ribs inward during the period of regeneration.

Usually there is a slight rise of temperature, pulse and respiration, which return to normal in a few days. A prolonged high temperature and rapid pulse indicate some serious complication, and such a patient deserves the best of symptomatic care. One patient, following the first operation, ran a high variable temperature and rapid pulse for some time, which was due to complications in the other lung that finally cleared up. This postponed the second operation for four months. It was followed, however, by an uneventful convalescence.

There may be quite a bit of pain in the operated area, which interferes somewhat with coughing; this should be controlled, because it is of prime importance that pulmonary drainage be kept up. Frequently the pain radiates into the breast and down the arm to the elbow, and results in restricted motion of the arm and possible loss of sensation in the hand and fingers. We have found these results to be purely temporary, and unless the scapula is fixed there is no interference with the function of the arm.

The patient may also complain of dyspnea, partly due to pain and partly to mediastinal flutter or poor heart action, because of the sudden change in intrathoracic pressure. Of course, the greater the amount of ribs taken out the greater will be the change in intrathoracic pressure.

This point should be carefully noted in determining the amount of ribs to be removed.

Results: In the most favorable cases we can expect to secure a collapse about equal to three-fourths of a good pneumothorax, so that the value of the thoracoplasty would be equal to a good partial pneumothorax less the shock and mutilation of the operation, which are not as great as one would expect. This should be borne in mind when advocating such a radical procedure.

The symptomatic improvement following the operation is often marked. Cough and expectoration decrease, weight increases, and the entire picture is changed. Some patients even have a firm conviction that they are cured. A decrease in sputum is a good prognostic sign, but it does not always mean that a cure has taken place. Tubercle bacilli may or may not disappear with the reduction in sputum.

Estimation of the success or failure of the operation from physical signs may be difficult, because one is dealing with a partially compressed lung and should be prepared to find almost any physical sign.

The percussion note may vary from slightly tympanitic to almost flat.

Bronchial and amphoric breathing, due either to uncollapsed cavity or to large bronchi, may persist permanently or for years.

Moist râles may persist for a time and may later become dry. This may be because the thoracic wall and the lung, to some extent at least, have lost their elasticity, and this event more or less prevents perfect pulmonary drainage. This should be remembered when one bases a prognosis on scanty expectoration and absence of tubercle bacilli, especially if found in connection with the above physical findings.

In time the operated side of the thorax falls in considerably, so that the edge of the scapula is visible from the front. Scoliosis may develop in the corresponding part of the spinal column. This will be just the opposite of what is found in empyema, the convexity being toward the well side, presumably because the muscles on the operated side have been partially paralyzed, due to cutting, and the muscles on the other side may draw the spinal column over. There will be little noticeable deformity when the patient is dressed. This is very important from the patient's point of view and aids the physician materially when he is trying to persuade the patient to submit to the operation. On the whole, one may well say that the inconveniences of the operation are small compared to its benefits.

We have had 12 cases at the Sanatorium and one case at the University Hospital. The Sanatorium cases were between 17 and 64 years of age. The duration of disease previous to the operation was from 19 months to 7½ years. The patients were under our care, previous to the operation, from 3 weeks to 32 months.

Of the Sanatorium cases 3, or 25 per cent, have died, one of them thirteen hours after the operation. This patient did not recover consciousness. I think the reason for this was that the heart or mediastinum could not accommodate itself to the sudden change in intrathoracic pressure. This was our first and last one-stage operation. One died five weeks after the operation. This patient had been receiving pneumothorax for several months but was failing steadily. A thickened pleura obscured the X-ray plate, and we were uncertain as to the exact condition, but thought that our pneumothorax must be unsuccessful, and we hoped that a thoracoplasty would improve her condition. Postmortem examination proved that the pneumothorax had been successful because the lung was well collapsed around a rather large firm-walled cavity which was partially filled with pus. From the autopsy findings I think we can safely say that the operation had no influence on the course of the disease. The third death occurred 17 days after the operation and was due to pus infection of the wound.

Nine, or 75 per cent, are living. Three, or 25 per cent, are unimproved, two of them because of tuberculosis of the ribs, which was recognized at operation. They are receiving heliotherapy while waiting for the second operation, and their prognosis is doubtful because of the pulmonary condition. The third has an increase of signs on the good side.

This leaves 6, or 50 per cent, that are more or less improved. Two have left the Sanatorium and are in excellent shape and two are progressing very favorably.

SUMMARY

Localized rest in addition to general rest is necessary for some patients. This can be partially obtained by medical measures and more completely by surgical measures. Of the latter, thoracoplasty is the most radical and therefore should be reserved for those cases in which the less radical measures, including pneumothorax, have been tried and have failed.

The two-stage is more desirable than a one-stage operation, and the ideal interval between the operations is not over three weeks.

CONCLUSIONS

Even though extrapleural thoracoplasty is a very extreme form of treatment, we must nevertheless remember that the patient has everything to gain and nothing to lose by the operation.

We may operate on some whose condition will not be improved, and this type of case will, of course, increase our mortality rate. But what is to be our primary aim:—Good statistical results or the possibility of helping some patient in whom the disease would otherwise continue to progress?

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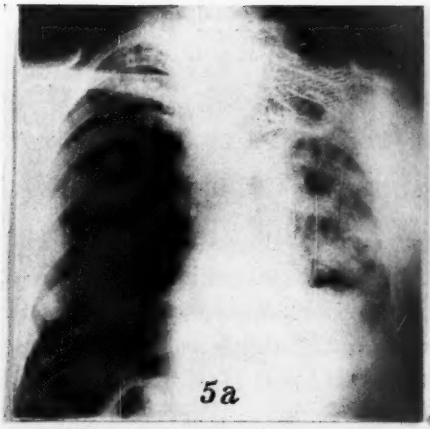

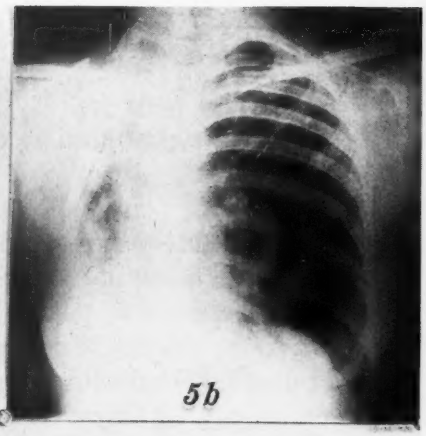

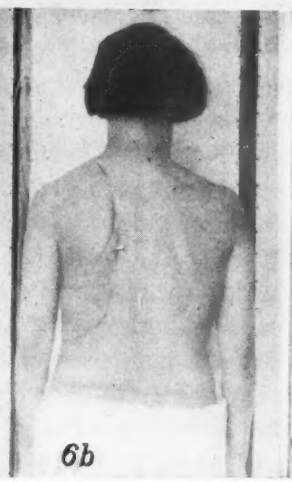

FIGS. 5a & 5b. RADIOGRAPHS SHOWING CONDITION BEFORE OPERATION AND COLLAPSE SECURED BY THORACOPLASTY

FIGS. 6a, 6b & 6c. TO SHOW THE SMALL AMOUNT OF DEFORMITY RESULTING FROM OPERATION AND NO NOTICEABLE DEFORMITY WHEN PATIENT IS CLOTHED

POSTPNEUMONIC CHRONIC PULMONARY DISEASE IN CHILDREN[1]

A CONDITION FREQUENTLY CONFUSED WITH TUBERCULOSIS

WILLIAM E. CARROLL, COLE B. GIBSON AND ANDREW BANYAI

No attempt will be made in this paper to discuss the differential diagnosis of pulmonary tuberculosis in general. Attention will be given only to the sequellae of pneumococcic, streptococcic and influenzal pulmonary disease with consideration for the differentiation of these chronic pulmonary conditions from tuberculosis. It is fully realized that this subject has been covered many times. Nevertheless, the fact that children suffering from nontuberculous pulmonary cirrhosis, chronic adhesive pleuritis, mild degrees of bronchiectasis, postinfluenzal chronic pneumonitis, etc., are frequently admitted to this sanatorium with the diagnosis of pulmonary tuberculosis, would warrant reopening the question.

These patients all have a cough of long duration with copious or moderate expectoration. It is because of these presenting symptoms that they are admitted. The age in the patients we have encountered ranges from ten to fourteen years. This is of importance because there is no difficulty in obtaining specimens of sputum for examination as there would be in younger children. The general condition of these patients is good; they are well nourished, afebrile and have no sense of malaise. The sputum is persistently negative for tubercle bacilli. On physical examination they present in the lungs numerous abnormal signs which are greatly at variance with the general good condition of the patient. Such a combination should immediately cause serious doubt that the child is suffering from pulmonary tuberculosis. This point has been emphasized by Packard, Stewart, McCrudden, Miller, Heise, Stivelman, White, Rist, Overend, Lawrason Brown and a host of other writers. Even so it is constantly overlooked.

During the last six years pneumonias of a mixed type have been common. The streptococcic and influenzal pneumonias have been chiefly

[1] Read at the Conference of the State Tuberculosis Commission, Meriden, Connecticut, October 6, 1924.

of lobular distribution. The exudate in pneumonias of this type will frequently organize instead of undergoing resolution, as in lobar pneumonia. Even in lobar pneumonia organization may take place. As a sequel there is a postpneumonic fibrosis of varying degree with consequent bronchiectasis. In lobular pneumonias which have come to autopsy Bakwin (1) found the pleura very frequently involved. These three conditions, pulmonary fibrosis, pleuritis and bronchiectasis, are the causes for persistence of symptoms and signs. The first two may exist in slight degree without symptoms. Many times, however, the fibrosis will cause cough and expectoration, and not infrequently bronchiectasis of greater or less degree will follow. Pleuritis when extensive, and especially in association with pulmonary fibrosis, will greatly limit respiratory movement, so that the chest on the side of the fibrosed lung appears greatly flattened. This train of events has been well described by Packard (2). It is here but briefly sketched.

We have encountered chiefly three types of cases. The most common has been a greater or less degree of unilateral pulmonary fibrosis, associated with pleural thickening and undoubtedly with adhesion of the visceral and parietal pleurae. The second type corresponds closely to the condition described by McCrudden (3) as postinfluenzal chronic pneumonitis. There has, however, been no marked nervous irritability. In the third type the predominating picture is one of bronchiectasis of moderate degree. These three syndromes will be considered in detail.

The following findings hold true for all three: All patients have had positive skin tuberculin reactions. This finding in patients of ten to fourteen years of age is without significance as a factor in differential diagnosis. Repeated negative tests would, of course, help in excluding tuberculosis. All have had persistently negative sputum by ordinary staining, by antiformin and sodium-hydroxide concentration methods and by guinea-pig inoculation. All have had negative Wassermann reactions. None has given evidence in the sputum of nocardiosis or of infection by the higher fungoid microörganisms. In all the blood picture has been without significance except for the occasional evidence of secondary anemia.

Pulmonary fibrosis with extensive pleuritis: Our patients of this type have been admitted because of cough, expectoration and asymmetry of the chest. In none has there been any known intimate exposure to sufferers from pulmonary tuberculosis. The history of past illnesses has been unimportant except for this notable fact. All have been in

good health until the onset of an acute respiratory disease from which they have been severely ill. After the acute illness, one usually diagnosed as "pneumonia," type not stated, has subsided, the child has continued to cough and expectorate for a period of from one to four or five years. In spite of the long-continued cough the patient is reasonably well nourished and does not present any symptoms of toxemia, such as hyperpyrexia, tachycardia, malaise, anorexia, etc.

On physical examination one side of the chest appears noticeably smaller than the other. On this side expansion is markedly limited throughout. The left side has been involved more frequently than the right. In most cases it can easily be demonstrated that there is deviation of the trachea toward the affected side. In one case this deviation was sufficiently marked to give physical signs resembling those of cavity at the left apex. Webb, Forster and Gilbert (4) have called attention to the ease with which this mistake can be made. In almost all cases the heart is displaced toward the affected side.

On percussion there is extensive and often universal dulness on the side involved. The breath-sounds are diminished in intensity compared with the better side, but are well heard throughout. They are in general of bronchovesicular quality. In some cases there have been areas of bronchial breathing along the lower half of the vertebral border of the scapula. There is usually increased whispered and spoken voice conduction. There have been mixed, small moist râles and crackling râles throughout the lung. The opposite lung shows little or nothing. Sometimes there are small moist râles below the angle of the scapula.

The X-ray findings have been remarkably constant. On the affected side there is a dense shadow due to pleural thickening. This sometimes extends from apex to base. In others it is more marked at the apex and the base, with a lesser degree intervening. In some the apex is clear with a dense shadow below. The disproportion in size of the two sides of the chest is very apparent; so also is that of the inclination of the trachea toward the side involved. The deviation of the heart shadow is very noticeable, especially in the patients with left-sided involvement. In most of these no heart shadow could be made out. It did not show at all to the right of the vertebral column and was lost in the dense shadow on the left side. Fluroscopy of such patients is interesting and in our patients has confirmed the interpretation made from the films. A point of great importance is that the opposite side shows little or nothing. In one or two patients there was evidence of pleural thickening at the

base. In none has there been cirrhous mottling or other evidence of parenchymal infiltration. The writers have never seen tuberculous disease involving one lung entirely without undoubted evidence of some tuberculous infiltration on the other side.

Chronic bronchopneumonic infiltration: We have used this term for want of a better one. McCrudden's *post-influenzal chronic pneumonitis* was a happy choice, but it is too exclusive for our purpose, since disability in some of our children dates from bronchopneumonias other than influenzal. This has been especially true of the bronchopneumonias following measles. Sante (5) has suggested *chronic diffuse interstitial fibrosis.*

Here we have a child with a history of cough and expectoration dating from a severe attack of influenza or of "pneumonia" of some kind. The duration of cough in our patients has varied from one year to four. Previous to the onset of acute respiratory disease the child had always been well. Since that time he has had continuous cough with slight or moderate expectoration in which tubercle bacilli cannot be demonstrated. The child does not appear ill and does not consider himself ill. Our patients have not presented the cardiac symptoms or nervous irritability described by McCrudden (3) in older patients. This, in the latter regard at least, may be due to a child's lack of introspection. They do however present a picture of severe, acute pulmonary infection "continued into chronic nonprogressive pulmonary disorder." The general condition is good; nutrition is good; there is no hyperpyrexia, tachycardia, undue fatigue or anorexia.

Physical examination: In contradistinction to the definitely unilateral lesions described above this type often shows abnormal signs on both sides. Resonance usually is not impaired. Sometimes there is dulness over one or both bases. In most of our cases there has been little or no change in the quality of the breath-sounds. Occasionally there is roughened respiration below the lower third of the scapula. As a rule there is no change in spoken or whispered voice conduction. One patient, however, presents definite signs of consolidation in the right middle lobe, showing dulness, bronchial breathing and whisper pectoriloquy over a sharply localized area in the fourth interspace anteriorly from the midline to the midclavicular line. The X-ray shows a heavy density in a corresponding location. No patients have shown increased whispered voice conduction at an apex.

The most constant finding is râles of various kinds and of varying

distribution. Most cases show a few scattered squeaky râles, with small moist râles in the lower third of one or both lungs. Râles are frequently heard at one or both apices, but are never confined to such a location; when they have occurred at an apex they have also been widely distributed throughout the lung. It frequently happens that they show variation in distribution at different examinations. Physical signs in general are never limited to the apices or upper lobes.

The X-ray helps greatly in excluding tuberculosis. Sometimes there are apparently normal findings. More often it is obvious that the films do not look normal, but one hesitates to make a definite diagnosis. In the various reports one finds such phrases as diffuse thickening, peribronchial thickening, small areas of increased density, infiltration of the lower lobes, hilum thickening, etc. The most important point is that X-ray evidence of abnormality is not characteristic of parenchymal tuberculous infiltration and that the apices are clear. In the patients who have shown râles at an apex there has been no roentgenological evidence of abnormality in this location.

Bronchiectasis: There is no doubt that many of the patients in the classes described above have some degree of bronchiectasis. Consideration will here be given to those instances in which bronchiectasis dominates the picture. It is not contended that juvenile bronchiectasis is invariably due to an antecedent pneumonia. Pertussis in early childhood, for instance, is known to be a frequent cause. Bronchiectasis occurring as a component part of established pulmonary tuberculosis is not under discussion.

These children give a history of long-continued cough, with copious thick yellow or greenish sputum in which tubercle bacilli cannot be demonstrated. The cough is periodic, and is followed by the expectoration of a large quantity of sputum. Then there is an interval of varying length during which there is freedom from cough. This interval may be of two or three hours' duration. The process is then repeated. In our patients these symptoms have persisted for a period of five to eight years, or for longer than the child can remember. There has been no progressive deterioration of health. In fact, the general condition is very good. With one exception all patients have been remarkably well nourished. Dyspnea on exertion has been present in some and absent in others. All have had clubbed fingers. All have had residual sputum after cleaning out the bronchial tract by coughing and then undergoing postural drainage. One patient has had slight blood-streaking. It must be

remembered that hemorrhage of greater or less degree is frequent in bronchiectasis.

The physical signs are variable and are not, of themselves, by any means characteristic. Changes in resonance have been slight; so also have changes in the quality of the respiratory murmur. The most constant finding has been a great profusion of small and medium-sized moist râles. In two patients these were distributed almost universally throughout both lungs. Usually they are limited to the lower lobe. We have found no increase in spoken or whispered voice conduction. No patients have had signs of cavity. It is, of course, true that bronchiectasis is usually a lower-lobe lesion. One patient, however, both from physical signs and X-ray evidence had undoubted bronchiectasis of the right upper lobe. This boy was under observation for four years. Throughout this period he showed slight impairment of resonance on the right side to the second rib in front and to the third dorsal spine posteriorly. There was no change in the breath-sounds or in whispered or spoken voice conduction. Medium-sized moist râles could always be heard to the fourth rib in front; sometimes they could be heard to the third dorsal spine posteriorly; sometimes they were absent. At other times râles were present throughout the whole right side posteriorly and in the axilla. The left lung was negative. Sputum was copious and purulent, and never showed tubercle bacilli. Repeated stereoscopic X-rays showed no mottling anywhere. On the right side above the level of the third rib there was well marked bronchial dilatation. The main descending bronchi on the right side appeared thickened.

The X-ray is an important diagnostic aid. There is no evidence of parenchymal infiltration compatible with the extensive physical signs. The bronchial markings are accentuated. We have found interruption of the bronchial markings to be a rather good indicator. Sometimes there is definite cylindrical dilatation. The hilum shadow is almost always increased. In general, abnormalities will be found in the lower part of the chest and the apices will be clear.

Bronchiectasis must be distinguished from pulmonary abscess and from chronic empyema communicating with a bronchus. If these conditions are borne in mind the differentiation should not be difficult.

CONCLUSIONS

1. Chronic pulmonary disease other than tuberculosis is not uncommon in children.

2. When signs are more manifest than symptoms tuberculosis is not a probable cause.

3. The proper grouping and interpretation of signs and symptoms are of more importance than the signs and symptoms themselves.

4. In a child, who presents a history of long-continued cough and expectoration without deterioration of health and with sputum persistently negative for tubercle bacilli, some condition other than tuberculosis should be sought as the causative factor.

5. Pulmonary syphilis and nocardiosis are very rare in children. Nevertheless, routine Wassermann reactions should be done, and search should be made for mycelial organisms in the sputum.

6. Pulmonary abscess and empyema communicating with a bronchus give definite clinical, physical and X-ray findings, and should be quite readily identified. The history is usually very suggestive.

7. In the absence of any of the conditions named above it is probable that disability is due to chronic postpneumonic fibrosis with or without extensive pleuritis and with slight or easily appreciable bronchiectasis.

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A PHYSICAL SIGN OBSERVED IN FIBROID PHTHISIS, FIBROUS PLEURISY AND INTERSTITIAL PNEUMONIA[1]

R. D. LILLIE[2]

The purpose of this paper is to call attention to a physical sign which has been observed in several cases with unilateral fibrosis of the lung or pleura. No mention of this sign is found in most modern text books on physical diagnosis, nor in several works on tuberculosis. Mention of its existence was made by Clark, Hadley and Chaplin (2), but not a detailed description.

The sign in question occurs in cases in which there is appreciable impairment of resonance over the lower part of the back on one side. It consists of a resonant area at the base next the spine. This area is generally triangular in form, wider at the base and coming to a point in the midspinal line above. In such cases as have only dulness near the base, the upper part of the triangle cannot be percussed. Even when there is no movement of the base of the lung on respiration, the base of this triangle often descends on respiration, sometimes as much as the other base, sometimes less.

The sign is associated with at least some, if not most, of the following other physical signs: Usually restriction of movement of that side of the chest, impaired resonance near the base posteriorly with weakened breath-sounds, which may occasionally be bronchovesicular in character and accompanied by increased whispered voice transmission. Fixation of the base is often present, and sometimes elevation above the level of the opposite side. Sometimes, also, there is very pronounced contraction of that side of the chest, with drooping of the shoulder and approach of the scapula to the middle line. Displacement of the heart to the affected side may often be demonstrated.

According to Laennec (1) the signs found in fibrous pleurisy with contraction of the lung are lack of normal percussion resonance and weakened breath-sounds on that side of the chest. The side of the chest itself is

[1] Published with the authority of the Surgeon-General, U. S. P. H. S.

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contracted, and the interspaces are narrowed. He cites four cases with post mortem findings:

> XXXII: A dense fibrocartilaginous pleural adhesion with tubercle in the lung. XXXIII: A dense fibrocartilaginous pleural adhesion with miliary pulmonary tubercle and ulcers in the intestines. XXXIV: A fibrinous deposit in the pleura with contraction of the chest while in the hospital, and recent tubercles in lungs and peritoneum. XXXV: Numerous pleural adhesions with two pints of fluid, tubercles in the pleura, pleuropulmonary adhesions of the apex and upper two-thirds of back, and atrophic hepatic cirrhosis.

Clark, Hadley and Chaplin (2) state, in part, that, as regards the physical signs on percussion in fibroid disease of the lung and pleura,

> usually the resonance is impaired throughout . . . . (the affected side) . . . . on the opposite, least affected side, if the disease (as is usual) is of one side only, an unusually good note may be obtained. Indeed, it is hyperresonant; and not infrequently this hyperresonance may be traced transgressing the middle line, both along the sternum in front and the spine behind.

This last sign is not described in any further detail, nor is it mentioned in any of their illustrative cases. They review the literature from Laennec up to 1894, and in these reviews there is no mention of resonance crossing the spine to the affected side.

Such texts on physical diagnosis and works on pulmonary tuberculosis as were available were consulted, and no mention of resonance crossing the spine in fibroid phthisis, interstitial pneumonia or fibrous pleurisy could be found. A list of the works consulted is given in the bibliography.

The sign under consideration has been found in some 16 cases, most of which were cases of pulmonary tuberculosis. Cases are cited herewith, with abstracts of the histories and X-ray findings, as well as the physical findings in detail.

The anatomic basis of the sign is probably similar to that of the Grocco sign, which is "possibly due to the bulging of the mediastinum by the fluid, across the middle line, the anatomic possibility of which has been pointed out by Calvert (Osler and McCrae (14)). In the case of the paravertebral resonant triangle it would be the bulging of the emphysematous sound lung across the middle line.

Case Reports

Case 1: J. L. Aged 25, ship's steward. Admitted February 25, 1924. *Family history:* Negative. *Past history:* Not significant as regards present illness. *Present illness:* Took cold about December 15, 1923. Productive cough, diminished somewhat since onset. Loss of 20 pounds since onset. Some night-sweats. Loss of strength and endurance, and shortness of breath coming on for past three months. *Physical examination:* Somewhat emaciated,

sallow. Throat raw. *Lungs* show flattening of upper chest anteriorly, dulness between 4th and 7th dorsal spines on both sides. Slight impairment of resonance below 7th dorsal spine, and one-inch elevation of base on right side. Both bases descend about one-inch on inspiration. On right side, diminished bronchovesicular breathing and increased whisper between 4th and 7th dorsal spines. Generally decreased breath-sounds in back. Numerous coarse râles, rubs, and squeaks below 5th dorsal spine to base, and fine râles between 4th and 7th dorsal spines. On left side, bronchovesicular breathing and increased whisper between 4th and 7th dorsal spines. No râles after cough. Tubercle bacilli found in sputum, February 27. Irregular fever 37° to 38.5°C. *X-ray*, February 28, showed clear right apex, faintly hazy left apex, mottling and infiltration of upper part of left lower lobe and right lower and middle lobes.

Examination of chest, April 5, 1924, in detail: Shape: Moderately broad and deep, right upper slightly flattened. *Mobility:* Restricted, especially on right. Apices retract on inspiration, especially right. *Fremitus* increased over right upper anteriorly and almost absent over right lower posteriorly. Palpable rub on left lateral to scapula. *Percussion: Right lung:* Dull below 3rd dorsal spine and 6th rib, very dull near base. Base fixed one-inch higher than left. Paravertebral triangle of resonance, with apex at 8th dorsal spine, and base is at same level as left base and descending one inch on inspiration. The base of this triangle is 1½ inches wide. Isthmus 3 inches wide. The dulness does not shift on change of position. *Left lung:* Dull between 3rd and 7th dorsal spines. Slightly impaired resonance below 2nd rib and 7th dorsal spine. Base moves one inch. Isthmus 3 inches wide. *Auscultation: Right lung:* Bronchovesicular sounds from 2nd to 4th dorsal spines, diminished below, almost absent at base (next morning breath-sounds below angle of scapula were distant and bronchial, with coarse dry râles, which persisted after cough, but were not brought out more clearly by cough). Bronchovesicular sounds between 6th and 7th ribs in axilla. Bronchovesicular, with râles in paravertebral resonant area. Whisper slightly increased between 3rd and 5th dorsal spines. No râles after cough. *Left lung:* Bronchial breathing 3rd to 6th dorsal spines; bronchovesicular below to base. Medium and coarse dry râles below 5th dorsal spine and 2nd rib, some of which persist after cough. Many musical rhonchi anteriorly. Whisper slightly increased above sixth dorsal.

Summary of physical findings: Infiltration of upper parts of lower lobes. Pleuropulmonary fibrosis right lower lobe. Fibrinous pleurisy left side.

In this case we would have decided that there was probably a pleural effusion on the right side, had it not been for the presence of the paravertebral triangle of resonance; and the reappearance of breath-sounds the next day confirmed our diagnosis of a dense fibrosis following a previous fibrinous pleurisy.

X-ray, taken two days later, showed mottling of the apex of the left lower lobe, left hilum and, to a lesser extent, the rest of the lower lobe. The right side showed a dense homogeneous shadow, 1½ inches wide, occupying the entire axilla at the level of the upper and middle lobes and apparently due to marked pleural fibrosis with possible exudate. The lower-lobe area was opaque. The heart was not apparently displaced.

Case 2: C. B. Marine engineer, age 32. *Family history and past history:* Negative. *Present illness:* Weakness and loss of weight began about September, 1923, and slight cough appeared about October first. Entered hospital October 22. Examination revealed lesion at right apex, without definite evidence of activity. Had no fever during five weeks under observation. Cough disappeared at time of admission. In December, 1923, acquired septic infection of left hand which lasted about three months. Entered another hospital, March 31, and while there had 50 cc. clear straw-colored fluid removed from right pleura. Diagnosed tuberculosis, on basis of physical signs, X-ray, effusion, fever, cough and slight expec-

toration. Readmitted to this hospital April 26, 1924, and examination on that date showed the following: Retraction of right apex, flattening of right upper chest, slightly winged right scapula, very distinct limitation of motion on right side and slight retraction of left apex. *Fremitus* diminished over right lower lobe. Cardiac dulness slightly displaced to the right. *Right lung:* Slight general impairment of resonance, more marked over back, in axilla behind 7th rib, and above 2nd rib in front; dulness below the angle of the scapula and above 3rd dorsal spine. Isthmus 1½ inches wide. Base fixed mesial to scapular line; moves 1½ inches in axilla and in front. There is a paravertebral resonant triangle, with apex at 6th dorsal spine and base 1½ inches wide and descending 1½ inches on inspiration. *Left lung:* Resonant. Isthmus 2½ inches wide. Base moves 1½ inches. *Breath-sounds* diminished throughout right lung; almost absent above 2nd dorsal spine and below angle of scapula; fainter in axilla and back than anteriorly; diminished bronchovesicular above 2nd rib anteriorly. Whisper slightly increased above clavicle and 2nd dorsal spine. Occasional fine moist râles after cough between 2nd and 4th dorsal spines. *Left lung:* Vesicular breath-sounds; slightly increased whisper, apex to 2nd dorsal spine; no râles after cough.

Diagnosis: Tuberculosis, chronic pulmonary, moderately advanced, active in right upper lobe, early fibrous pleurisy of right side. X-ray examination, April 28, showed pulmonary tuberculosis of right upper lobe, with thickened pleura and probably mild effusion at right base.

Case 3: B. Y. Filipino; fireman, age 34 years, chronic discharging empyema, left side, since 1918. In hospital since January, 1922. Diagnosed tuberculosis, but has had 50 negative examinations for tubercle bacilli. Slight irregular fever from time to time. *Physical findings,* April 11, 1924: Entire left side flattened and contracted. Spine scoliotic, concave to the left. Left shoulder lower. Left scapula 2 inches from the spine, right 4 inches. Mobility slight on left, moderate on right. Sinus discharging sanguino-purulent fluid below and lateral to angle of left scapula. Tactile *fremitus* diminished on left side. Right border of cardiac dulness ½ inch to left of midsternal line; left border one inch to left of nipple line. *Right lung:* Impaired resonance above 3rd dorsal spine and 1st rib, and below 3rd intercostal space and mesial to right nipple line. Isthmus 1½ inches wide; does not expand. Base descends 2½ inches on deep inspiration. *Left lung:* Resonance good between 1st and 4th ribs anteriorly; remainder impaired; dull above 2nd dorsal spine and between midaxilla and scapular line. Isthmus obliterated. Base fixed. There is a paravertebral resonant triangle, with apex at 6th dorsal spine and base 1½ inches wide and descending 2½ inches. *Breath-sounds* of right lung bronchovesicular above 2nd rib and 2nd dorsal spine; otherwise emphysematous. Increased whisper above 2nd interspace and 6th dorsal spine and below 4th rib mesial to nipple line. No râles after cough. *Left lung:* Breath-sounds absent between midaxilla and scapular line, diminished over entire back, bronchovesicular above 1st rib, and diminished below 4th rib. Whisper increased above clavicle, below 4th rib, and markedly over entire back. Distant bronchial whisper in axilla and about the discharging sinus. After cough a few medium râles heard below 4th rib and 7th dorsal spine. *X-ray examination,* April 12, 1924, showed slight infiltration of right apex and 1st interspace; obliteration of right costophrenic sinus for a distance of about one inch; slight traction and displacement of trachea to left; and marked pleural thickening of the left base and, to a lesser extent, of entire left side.

Case 4: J. A. Marine fireman, age 41. *Family and past history:* Negative. *Present illness:* Entered hospital, July 31, 1923, with pneumonia of left lower lobe and pleurisy on left side, which subsided by lysis. From August 14 to 17 had septic fever up to 41°C. Purulent expectoration with low fever and 26,000 leucocytosis, was noted about September 1, and

this became foul and greenish-yellow during next two weeks. X-ray showed fluid level at left base. *Pulmonary hemorrhage* occurred first on October 2. A shadow in the left lower lobe, noted October 19, was considered as a possible abscess by the roentgenologist, but this shadow was absent on November 5. Patient's temperature was normal during October. *Hemoptysis* recurred November 30, followed by fever for two days. On December 21 the patient was transferred to the tuberculosis service for observation. *Physical and X-ray findings* at that time were as follows: *Chest* broad, deep and symmetrical. *Mobility* slightly restricted on left side. *Fremitus* diminished over both upper lobes, but present throughout. Cardiac apex beat in 5th interspace in nipple line. *Percussion: Right lung:* Slightly impaired resonance above 2nd rib and 5th dorsal spine. Base moved 1½ inches. *Left lung:* Slight general impairment of resonance, definitely impaired note above 2nd rib and 4th dorsal spine, dull below 8th dorsal spine and behind 7th rib. Base fixed. There is a paravertebral resonant triangle, 1¼ inches wide, at the base. *Auscultation: Right lung:* Diminished breath-sounds above 2nd rib, vesiculobronchial, apex to fourth dorsal; slightly increased whisper over apex; no râles after cough. *Left lung:* Breath-sounds diminished throughout, very faint below angle of scapula, roughened in second interspace, and roughened bronchovesicular about 3rd dorsal spine. Whisper somewhat increased along left side of spine and below 6th dorsal spine and angle of scapula. No râles after cough.

Diagnosis: Interstitial pneumonia, slight, left lower, with lung abscess or bronchiectasis. *X-ray examination* shows dense homogeneous shadow, about size of hen's egg, in region of left lower bronchus, probably abscess, and obliteration of left costophrenic sinus.

Subsequent course: High, septic fever from December 25 to 30, with 250 to 300 cc. of very foul, purulent sputum daily. After this, fever disappeared, and expectoration diminished with, however, occasional blood-staining, until now (April 22) it is very slight. Thirty-five examinations of the sputum have failed to reveal tubercle bacilli.

Examinations have shown partial liberation of the left base with, however, still persistent paravertebral triangle of resonance. The abscess shadow in the left lower lobe has disappeared, leaving "only a residual scar."

Examination, April 23, 1924, showed persistent fixation of left base posteriorly, but not laterally nor anteriorly, a small paravertebral resonant triangle on the left, the base of which moved 1½ inches, bronchovesicular breathing and medium and coarse moist râles and post-tussive suction in the dull area previously noted at the left base posteriorly.

CONCLUSIONS

A paravertebral resonant triangle at the base on the dull side has been found in certain cases giving other physical signs and X-ray evidence of unilateral pleural or pulmonary fibrosis. This sign is believed to be of aid in differentiating the dulness due to these conditions from that due to effusions and consolidations (as in caseous pneumonia). No cases of lobar pneumonia were examined with this point in view and such cases are usually too sick to permit of very detailed examination.

Note: Since the above was written the author has seen a case which showed dulness, diminished fremitus, and diminished but not absent breath-sounds at the right base posteriorly. The base was fixed at the expiratory level of the opposite side. There was a paravertebral resonant triangle at the base, the base of which descended about 1½ inches. X-ray taken shortly afterward showed evidence of effusion, and about 200 cc. of clear straw-colored fluid

was aspirated. It is believed that there must have been some preëxisting adhesions in this case. This case of effusion is one that did not give the classical signs of fluid, but gave signs that would indicate a thickened pleura.

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THE VITAL CAPACITY IN PULMONARY TUBERCULOSIS[1]

WITH SPECIAL REFERENCE TO ITS PROGNOSTIC SIGNIFICANCE

BARNET P. STIVELMAN AND RAPHAEL A. BENDOVE

Due to the evolution of accurate scientific methods in the past few decades, the estimation of the functional capacity of vital organs has deservedly come to play a very important part in all branches of clinical medicine. That tests of the functional capacity of such important and frequently diseased organs as the lungs should, until very recently, not have engaged the interest of clinicians, is difficult to explain. This is all the more surprising in view of the fact that as early as in 1846, Hutchinson (1) gave a very fine description of his extensive researches in the methods and value of spirometry in various lung affections. Nor did Arnold's (2) valuable contribution to this subject in 1855 act as a stimulus to workers in this field.

However, it is not our intention to expatiate on the probable reasons why even to-day only a lukewarm interest is exhibited in the vital capacity estimations in lung disease, but rather to add to the data already accumulated relative to the diagnostic and prognostic value of the determination of the functional capacity of the lungs in the various stages and protean manifestations of pulmonary tuberculosis.

While there is as yet no unanimity of opinion regarding vital-capacity standards, a review of the literature indicates that Dreyer's (3) tables are most satisfactory for all clinical purposes. Myers's (4) charts are valuable, but because they do not provide for the classification of patients into the various types of physical fitness depending upon occupation and mode of life, they are somewhat more time-consuming. In the use of Dreyer's tables we felt that the data discernible from chest-circumference measurements would be of little value because, on the one hand, it is difficult to rely on the patient to keep his chest in mid-expiration or mid-inspiration while this measurement is taken and, on the other hand, it is not applicable with any degree of accuracy in the case of women, or in those whose chests are contracted as a result of unilateral disease or distorted because of spinal curvatures.

[1] From the Bedford Sanatorium for Tuberculosis, Bedford Hills, New York.

The estimation of vital capacity by means of surface area has been suggested as the most dependable of all methods. Recent investigations, however, have shown that even with this method no definite standards have yet been set. West (5) found that in women the relation of vital capacity to the area of body surface is 2 litres per square metre, while Myers found this relation to be 1.87. Moreover, in spite of the fine tables for computing surface area from weight and height measurements prepared by DuBois and DuBois (6), this method is more time-consuming than the other equally dependable ones.

We have, therefore, utilized Dreyer's tables as shown in his excellent monograph and have depended mainly on the stem-height and weight measurements. The stem-height measurements were taken in accordance with Dreyer's suggestion, namely, with patients sitting on the floor, and erect against the wall on which a scale graduated into quarter-inches was appropriately attached. The weights, to avoid mistakes that would occur in cases of obesity or malnutrition, were in each instance corrected in accordance with the tables of standard weights, for height and age, of the Prudential Insurance Company of America. The percentages of the normal vital capacity obtained by both means were added and divided by 2 to obtain the final value in each case.

In our study we used the Sanborn water spirometer made in accordance with the suggestion of Peabody and Wentworth (7). We found this instrument entirely serviceable and accurate for all clinical purposes. Each patient was thoroughly instructed in the use of the spirometer, and the highest of at least three readings obtained with the patient standing was accepted as the vital capacity. In newly admitted patients, however, the figure obtained on reëxamination seven to ten days after admission was taken as the true vital capacity. In this way we did away with errors which would have occurred as a result of the patient's nervousness, and also avoided the initial fall in vital capacity as observed by Cameron (8) and ascribed by him to change of climate and environment. Subsequently, the vital capacity was estimated in connection with the routine reëxamination of all patients every six weeks and as often as the case demanded when complications or activity supervened.

The average length of observation of the 377 patients which form the basis of this communication was eight months, with a range of four to eighteen months. Those who remained at the sanatorium for less than four months were not included in the tables dealing with the prognostic value of the test.

With few exceptions our patients, having led a very inactive life and having been mainly employed at sedentary occupations, naturally fell in class *C* of Dreyer's tables. In the few instances in which the physical fitness of the patient warranted a higher rating the vital capacity was computed in accordance with the figures in class *B*.

The classification of the National Tuberculosis Association was strictly adhered to, both as regards condition on admission and on discharge, and the Rathbun modification relating to the degree of clinical activity was utilized advantageously. Each and every case was subjected to frequent roentgenographic examination in order to study the progress

TABLE 1

Showing the relation of vital capacity to the extent and activity of the lesion, "A" signifying little or no clinical activity, and "B" moderately severe clinical symptomatology

	MALE					FEMALE				
	Activity					Activity				
	A			B		A			B	
	Total	Number	Vital capacity	Number	Vital capacity	Total	Numoer	Vital capacity	Number	Vital capacity
			per cent		*per cent*			*per cent*		*per cent*
Stage I	18	18	97.4			17	17	95.8		
Stage II	73	69	91.4	4	65.8	47	36	85	11	66.2
Stage III	121	86	74.1	35	64.6	69	39	69.2	30	57.9
Doubtful	20	20	100.1			12	12	94.8		
Total	232					145				
	377									

of the lesion, and the entire series does not include a single case in which the diagnosis on discharge was doubtful.

Table 1 was computed from the vital-capacity estimations of 377 patients on admission to the sanatorium. It shows the relation of vital capacity to the degree of anatomic involvement or stage of the disease as well as to the clinical activity of the lesion, *A* signifying little or no clinical activity and *B* moderately severe clinical symptomatology. Analysis of these figures discloses that patients admitted with a doubtful diagnosis but discharged as definitely nontuberculous had a vital capacity within normal limits, the average in the case of male patients being 100.1 per cent and in females 94.8 per cent.

TABLE 2

Showing the relation of the vital capacity to the immediate prognosis in 284 discharged patients

CONDITION ON DISCHARGE		MALE							FEMALE						
		Vital capacity increased	Vital capacity stationary	Vital capacity decreased	Percentage of patients with vital capacity increased	Average gain in vital capacity	Percentage of patients with vital capacity decreased	Average loss in vital capacity	Vital capacity increased	Vital capacity stationary	Vital capacity decreased	Percentage of patients with vital capacity increased	Average gain in vital capacity	Percentage of patients with vital capacity decreased	Average loss in vital capacity
Stage I	Arrested and apparently arrested	11	4	0	75	9	0	0	7	3	0	70	8	0	0
	Quiescent and improved	1	0	0	100	6	0	0	1	0	0	100	6	0	0
	Unimproved and progressive	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stage II	Arrested and apparently arrested	19	6	0	76	10	0	0	9	4	4	53	4.8	23.5	4.2
	Quiescent and improved	13	7	5	52	4.5	20	3	6	6	3	40	1.5	20	10.3
	Unimproved and progressive	2	2	2	33.3	2	33.3	36.5	0	1	7	0	0	86	19
Stage III	Arrested and apparently arrested	12	8	3	52.2	5.2	13.4	6.5	5	2	0	71.4	7	0	0
	Quiescent and improved	30	7	7	68.2	8.9	16	5.5	9	8	8	36	9	32	16.3
	Unimproved and progressive	10	3	18	32.3	1.2	58.1	10.2	4	9	18	12.9	4	58.1	9

In patients with minimal disease the vital capacity readings were practically within normal limits, namely, 97.4 per cent in males and 95.8 per cent in females.

In moderately advanced disease with grade *A* activity, the vital capacity in male patients averaged 91.4 per cent and in females 85 per cent. It was different, however, in the case of stage 2 patients with grade *B* activity. Here, although the number of patients observed was small, the marked decrease in the functional ability of the lungs was so marked as to merit our close attention. The average in the case of male patients in this group was 65.8 per cent and in females 66.2 per cent.

The figures obtained in the case of far-advanced patients show that the average vital capacity in male patients with *A* symptomatology was 74.1 per cent and in females 69.2 per cent. With *B* activity the male patients of this group showed an average of 64.6 per cent vital capacity and the females 57.9 per cent.

It is seen therefore: *1.* That in minimal disease the vital capacity is practically within normal limits, as evidenced by the values obtained in the nontuberculous patients who were naturally of the same type and physical endowment. *2.* That the vital capacity diminishes with the advance of the structural involvement of the lungs, being lowest in patients with far-advanced disease. *3.* That the vital capacity is often more markedly affected by the degree of clinical activity than the extent of the anatomic lesion. Thus, patients in the *2B* group had a lower vital capacity than those in class *3A*.

Scrutiny of table 2 reveals data which, while not entirely unanticipated, are nevertheless very interesting and instructive. It shows that no patient with minimal disease on admission, who has been discharged with disease arrested or apparently arrested, has lost in vital capacity, and that 75 per cent of male patients have gained an average of 9 per cent in vital capacity and 70 per cent of female patients an average of 8 per cent. The two patients in this group who were discharged with condition quiescent also showed a gain of 6 per cent.

It is different in the case of patients who were admitted with moderately advanced disease. While the male group in this class who were discharged arrested or apparently arrested made similar gains to those admitted with minimal tuberculosis, namely, 75 per cent having gained 10 per cent in vital capacity, only 53 per cent of female patients made an average gain of 4.8 per cent, and 4 patients have actually lost an average of 4.2 per cent in vital capacity.

When we come to patients with moderately advanced tuberculosis, who were discharged quiescent and improved, we note that 52 per cent of the male patients gained an average of 4.5 per cent in vital capacity, while an insignificant gain (1.5 per cent) is recorded in the case of 40 per cent of the females. In this small group there were also 5 males who lost an average of 3 per cent and 3 females whose vital capacity decreased by an average of 10 per cent. In the few patients in this group discharged unimproved and progressive, there was, as we would expect, a decided decrease in the vital capacity; in the case of males, an average loss of 36 per cent and in females, 19 per cent.

Analysis of the figures relative to patients admitted with disease far advanced, clearly indicates the prognostic value of vital-capacity estimation. Fifty-two per cent of the males and 71 per cent of the females of

TABLE 3

Showing the prognostic value of the initial vital-capacity reading in far-advanced cases as compared with the estimation of clinical activity on admission

CONDITION ON ADMISSION (STAGE III)	CONDITION ON DISCHARGE			
	MALE		FEMALE	
	Improved	Progressive	Improved	Progressive
"A"	83.8	16.2	81.6	18.4
"B"	34	66	30.4	69.6
Vital capacity above 70	74.2	25.8	61.3	38.7
Vital capacity below 70	43.6	56.4	40.6	59.4

Note: In the case of females the figures below and above 65 per cent were taken in this table.

the small group of patients, who in spite of the advanced character of the disease were fortunate enough to leave with disease arrested or apparently arrested, gained an average of 5.2 per cent vital capacity in the case of the former and 7 per cent in the case of the latter; while 13.4 per cent male patients in this group lost an average of 6.5 per cent. It is extremely interesting to note that contrary to expectation those in the male group, discharged with condition quiescent and improved, did as well in so far as the vital-capacity estimation is concerned as the group discharged with disease arrested. Here 68 per cent of the patients gained an average of 8.9 per cent, while 16 per cent lost an average of 5.5 per cent. On the other hand, only 36 per cent of the female patients gained an average of 9 per cent, and 32 per cent of them lost an average of 16.3 per cent. However, when we come to the large number of patients in the group who left with disease unimproved or progressive, we note

that 58 per cent of the male patients lost an average of 10.2 per cent, and a similar percentage of female patients lost an average of 9 per cent, while very few have made insignificant gains.

It is apparent, therefore, that the results of vital-capacity determinations bear a definite relation to the stage of the disease and condition on discharge. The highest proportion of patients who show the highest increase in vital capacity are almost always to be found among those who suffered from limited tuberculous involvement, with slight or no activity on admission, and who were classified as arrested or quiescent on discharge. On the other hand, the greatest number who show the greatest losses in vital capacity are to be found among those who were admitted with advanced and active disease and failed to improve, or grew progressively worse in spite of treatment.

While the initial vital capacity has little prognostic value in the earlier stages of the disease, it is different in the case of patients with advanced pulmonary trouble. Table 3 shows that male patients with vital capacity above the average for the group did as well as those admitted with *A* symptomatology. Seventy-four per cent of the former and 83 per cent of the latter showed improvement as a result of treatment, while 25 per cent of the former and 16 per cent of the latter failed progressively in spite of care. A similar condition obtained in the case of female patients, 81 per cent of those admitted in class *A* and 61 per cent of those with vital capacity above the average for the group did as well, and 18 per cent in the case of the former and 38 per cent in the case of the latter did not profit by treatment. On the other hand, those admitted with vital capacity below the average for the group did as poorly as those who came with symptomatic classification of *B*. In the case of the male patients with *B* symptomatology, 66 per cent lost ground and 34 per cent showed some improvement; while those whose vital capacity on admission was below the average showed progressive disease in 56 per cent and improvement in 43 per cent. In the female group those with *B* symptomatology showed progressive disease in 69 per cent and improvement in 30 per cent of cases; while in the patients whose vital capacity was below the average, there was recorded progressive disease in 60 per cent and improvement in 40 per cent.

DISCUSSION

That there occurs a reduction in the vital capacity in pulmonary tuberculosis, and that this reduction is more pronounced with the advance-

ment of the lesion, has been noted by many workers in this field. But that the functional ability of the diseased lung is often more profoundly affected by the character rather than the extent of the structural involvement has received scant attention.

Our studies show that, regardless of the extent of the anatomic involvement on admission, those who were discharged with disease arrested or apparently arrested showed a persistently increasing vital capacity, or if the vital capacity was high on admission it remained practically stationary. On the other hand, those who were discharged with condition unimproved or progressive showed, in the great majority of instances, a persistently declining vital capacity; or, as was observed in some instances, a markedly fluctuating vital-capacity curve.

Our figures also reveal that moderately advanced active cases on admission show an average vital capacity much lower than far-advanced inactive patients, so that one is led to assume that factors other than the degree of structural involvement play an important rôle in the functional ability of the lung. Moreover, these serial spirometric measurements suggest that the functional compensation of the lung occurs much in advance of the actual healing of the lesion or arrest of the disease process, as is evidenced by the fact that those patients, regardless of the of the stage of the disease, who still harbored tubercle bacilli in their sputum and were classified quiescent on discharge, did as well, in so far as their increase in vital capacity was concerned, as those who left with disease arrested.

Just how an active lesion brings about a greater curtailment in the vital capacity than an inactive lesion of similar size can at present only be conjectured. There can be no doubt that this decrease is at least partially due to the reflex inhibition of the respiratory movements incident to toxemia as well as to those inhibiting effects directly traceable to points of local irritation. On the other hand, the local edema and congestion, that is, the collateral inflammation, which constitutes the usual reaction to new tuberculization by collapsing adjacent alveoli, further diminishes the functionating area of the lungs. There is also evidence that the increase in carbon-dioxide tension secondary to active lung processes curtails the expiratory phase of respiration, and thus further encroachment is made on the vital capacity. To these may be added mechanical factors, such as excessive secretion and plugging of bronchioles with mucopurulent material, which diminish the ingress and egress of air from corresponding alveoli.

A sharp and marked reduction in the vital capacity may be due either to pleural or pulmonary complications. In the former group spontaneous pneumothorax and pleurisy with effusion are most commonly met with. When an effusion supervenes, the degree of the decrease in the vital capacity is directly proportional to the extent of the exudate; and the rapidity with which the vital capacity returns to normal is a safe guide in judging the degree of its absorption. In some cases, probably due to the beneficial effects of the compression of the lung lesion by the effusion, the vital capacity ultimately reaches a higher level than prior to the occurrence of this complication.

Tuberculous pneumonia, as seen in massive involvement or secondary to hemoptysis, is the most frequent cause of a sharp and sudden drop in the vital capacity due to pulmonary complications. In 2 of our cases the diminution amounted to 50 per cent. Here, as in the case of effusion when recuperation occurs, the vital capacity mounts slowly and approaches the normal within three months. In both instances, it is the toxic and mechanical factors incident to the complicating condition that are responsible for the reduction in the vital capacity. This reduction should not be confused with the fluctuating type of vital capacity, as seen in patients with progressive lesions or in those with fibroid phthisis.

It should be emphasized that it is the serial vital-capacity estimations which give valuable data regarding prognosis in the individual case, and that in most instances a single reading, while determining the extent of structural involvement and frequently the temporary clinical status of the case, has little prognostic significance. However, in the case of patients with far-advanced disease, if the initial vital-capacity reading is lower than the average for this group, the prognosis, as our studies reveal, is decidedly less favorable than in patients with similar involvement whose initial vital capacity is equal to or above the average for the group. In this respect a single vital-capacity estimation is almost as valuable as the estimation of the clinical activity of the lesion. The two taken together, however, will greatly minimize the chance of prognostic error.

The diagnostic value of the estimation of the vital capacity in pulmonary tuberculosis is very limited indeed. In cases with inactive minimal disease we have noted that the vital capacity suffers no diminution whatever and, while the functional ability of the lung as evidenced by spirometric tests suffers materially with the advancement in the

pulmonary involvement, the decrease in the vital capacity in such cases does not necessarily point to any etiological relationship. Indeed, such curtailment in the functional ability of the lungs is seen in most non-tuberculous pulmonary disease as well as in many cardiac affections.

SUMMARY

1. Serial vital capacity estimations were made on 377 patients who remained at the Sanatorium from 4 to 18 months.

2. The percentage of the normal vital capacity was computed from Dreyer's tables, utilizing the stem-height and weight measurements. The latter were corrected according to the tables of standard weights for height and age of the Prudential Insurance Company. The average of the figures obtained by the two measurements was accepted as the true vital capacity in each case.

3. Tables were prepared to show (a) the relation of vital capacity to the degree of the anatomic involvement of the lungs and to the activity of the lesion, (b) the effect of sanatorium treatment on the vital capacity, and (c) the prognostic value of the initial spirometric reading in far-advanced disease.

4. While the vital capacity decreases progressively with the advancement of the lesion, it remains practically normal in inactive minimal disease.

5. The activity of the lesion exerts a marked influence on the vital capacity, reducing it further than would be expected from the anatomic involvement alone. This reduction, however, is not permanent and disappears with the abatement of the clinical activity.

6. Pleural and pulmonary complications cause a sharp decline in the vital capacity which, however, increases gradually with the recovery from such complications.

7. Vital capacity estimations on discharge disclose that, regardless of the degree of the anatomic involvement on admission, the great majority of patients discharged with disease arrested or apparently arrested show a decided increase in their vital capacity. Similar conditions obtained in the case of patients discharged with condition quiescent or improved. There was, however, a very decided loss in the vital capacity in those who left with disease unimproved or progressive.

8. A single vital capacity is of little prognostic value except in those suffering from far-advanced disease, whereas on admission it has almost the same prognostic significance as the estimation of clinical activity.

9. Serial spirometry shows (a) that those who have a stationary or a persistently increasing vital capacity do very well under sanatorium care, (b) that those who have a fluctuating or a persistently decreasing vital capacity do poorly as a rule, and (c) that the reduction in the vital capacity due to complications is not necessarily of unfavorable prognostic import.

10. Because the vital capacity in minimal tuberculosis suffers no diminution and because many nontuberculous lung conditions, as well as cardiac affections, markedly decrease the functional ability of the lung, spirometry is of very little value in differential diagnosis.

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STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE[1]

XIX. THE SIGNIFICANCE OF SERIAL VITAL-CAPACITY READINGS IN THE GUIDANCE OF DIAGNOSIS AND TREATMENT OF CERTAIN DISEASES OF THE CHEST[2,3]

J. A. MYERS

The importance of the detection of early disease, as well as the prevention of disease, has long been appreciated by those doing health work. Perhaps there has never been a time when the public has been so responsive to good-health teaching as the present. Therefore, this is a logical time to launch movements which will aid the public in obtaining and retaining that most valuable asset, good health; and also to decry movements promoted by the unprepared and untrustworthy who only too often seek personal financial gain at the expense of public health. For a long time body-weight has been looked upon as an index of good health. We know that it is materially changed by certain disease conditions, some resulting in its increase but the majority in its decrease. Although this is true, one meets many people who know nothing of their actual body-weight. On the other hand, there are many persons who, because of past public-health education, pay a great deal of attention to their weight and become concerned when deviations from the usual are observed. The importance of encouraging all persons to keep body-weight records is obvious.

An equally valuable criterion of good health is the vital capacity of the lungs, which is easily determined, and is remarkably constant from year to year in adults before the age of forty-five, except in the presence of disease involving directly or indirectly the heart or lungs. Therefore, if one's actual vital capacity is known it may serve as an excellent

[1] From the Department of Internal Medicine and the Department of Preventive Medicine and Public Health, University of Minnesota, Minneapolis.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

[3] Presented in part before the medical staff of the Lymanhurst School for Tuberculous Children, June 24, 1924.

standard of judging the condition of these organs from time to time. In children the vital capacity increases with body-growth, but there is such a definite correlation between body-size and vital capacity in childhood that one is able to anticipate with a reasonable degree of accuracy the increase in vital capacity with a given increase in body-size. As long as the vital-capacity increase is consistent with the increase in body-size there is no cause for alarm. The following cases illustrate this point:

A girl of 15 years had recently lost a twin sister from pulmonary tuberculosis. Her parents, being very solicitous of her health, demanded that her lungs be carefully examined from time to time. On the first examination her weight was 121 pounds and her vital capacity was 2900 cc. No phase of the physical or X-ray examination revealed any evidence of disease of the lungs or heart. Three years later her weight had increased to 145 pounds, and her vital capacity had increased to 3500 cc. Reëxamination of the heart and lungs revealed no evidence of disease. The confirmatory evidence obtained from the vital-capacity readings in this case was very helpful.

A boy of 15 years had been told by his family physician that an examination revealed slight evidence of early pulmonary tuberculosis. Soon after this examination the boy's weight was found to be 120 pounds and his vital capacity was 3400 cc. (fig. 1). Four months later his weight had increased to 130 pounds and his vital capacity to 3600 cc. One year after this his weight was found to be 138 pounds and his vital capacity 4000 cc. Examination at this time revealed no evidence of pulmonary tuberculosis.

Another case is that of a school boy of 14 years who developed empyema. His weight was 76 pounds and his vital capacity 2000 cc. (fig. 2). After about 10 weeks of treatment his body-weight had increased to 86 pounds and the vital capacity to 2400 cc. Two years later his weight was found to be 115 pounds and his vital capacity 2700 cc. Approximately four months after this the weight had increased to 126 pounds and the vital capacity to 3200 cc.

If, on the other hand, the vital capacity of the lungs of growing children decreases or even remains constant in the presence of definite increase in body-size the evidence is sufficient to warrant most careful examination and subsequent observation for disease of the lungs or heart.

The extensive observations of Stewart (1) on the vital capacity of the lungs of children led him to believe that the maximum capacity of boys is reached about the age of 20 years while in girls it is reached slightly earlier. After this age the vital capacity normally remains quite constant until such bodily changes as the loss of elasticity of the lung tissue begin to occur. Then the vital capacity begins to decrease, and continues to decrease slowly as age advances. The time when this begins is subject to considerable individual variation. Usually, however, it is not very marked before the age of 45 years.

Since vital lung capacity is such a constant factor in a given person it is obvious that it should be recorded for as many persons as possible.

Unfortunately, not many people now have on record their actual vital-capacity readings; consequently, we are compelled to employ theoretical normal standards which, like body-weight standards, are usually derived from averages and also, like weight standards, can never be highly satisfactory because of individual variations. However, until the time arrives that the actual readings of large numbers of persons are on record, we must select and use the best available standards. Observations have shown that there probably exists a closer correlation between body surface and vital capacity than any other measurement. We are deeply indebted to DuBois and DuBois (2), as well as to Boothby and Sandiford (3), for graphic charts which now make it possible to ascertain the body surface, when height and weight are known, without the use of any mathematical calculations.

Tables (4) have been prepared from which one, knowing the surface area and the actual vital capacity of a person, may ascertain the percentage of the theoretical normal vital capacity without the use of mathematical formulae. Tables (5) were published in an earlier paper which require only the body-weight and the vital capacity of the patient for their use. In the examination of more than 12,000 persons at the University of Minnesota we have found that both of the above mentioned tables give approximately the same results. West (6) has shown that for rapid clinical work a standard based on the height of the patient is reasonably satisfactory. Tables (7) have also been published which make it possible to ascertain the percentage of the theoretical normal vital capacity of a patient when only the height and capacity are known.

As previously stated, because of individual variations some normal persons have vital capacities considerably higher, and others lower than the theoretical normal. Obviously, in such cases the vital-capacity test cannot be of great value in diagnosis when a single reading is taken. However, if previous readings taken when such persons were in good health are available, this test is of tremendous value when examining for disease. The following cases are cited to illustrate this point:

A young woman of 20 years was enrolled as a freshman medical student when without warning she had a frank hemorrhage. Physical and X-ray examinations made in December, 1920, revealed a very definite parenchymatous involvement of the left upper lobe while the laboratory examination disclosed numerous tubercle bacilli in the sputum. Her vital lung capacity was not taken until May, 1921, when it was found to be 2500 cc. (fig. 3). A record was available of an examination made in September, 1920, which presented no evidence of disease of the lungs. At that time her vital capacity was 3276 cc. After treatment had brought about an arrest of her tuberculosis this patient completed an arts and science course.

Figure 1
TUBERCULOSIS SUSPECT

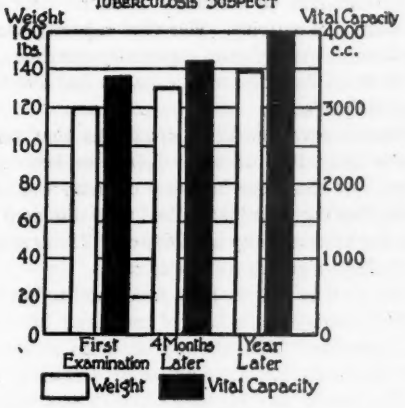


Figure 3
PULMONARY TUBERCULOSIS

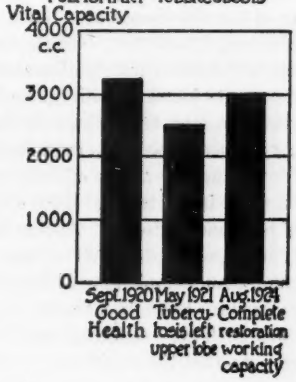


Figure 2
EMPYEMA

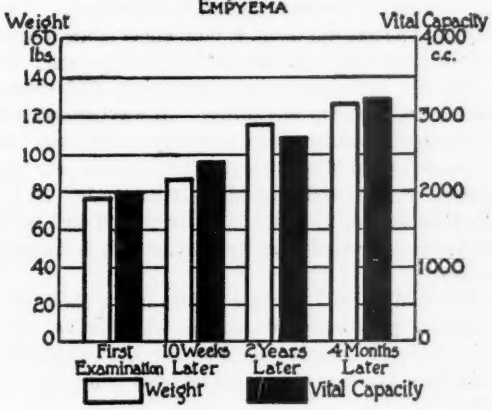


Figure 4
PULMONARY TUBERCULOSIS

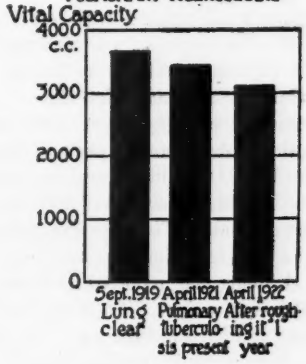
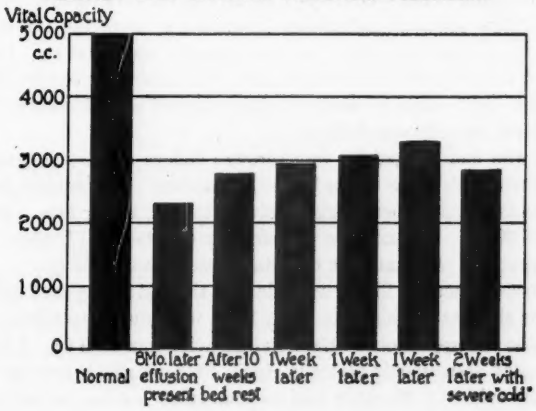


Figure 5
PLEURISY WITH EFFUSION FOLLOWING PNEUMONIA



She is now employed as a teacher. An examination on August 9, 1924, revealed definite evidence of the old disease area but no evidence of activity. Her vital capacity was found to have increased to 3000 cc. The patient is now classified as an apparently cured case. This case illustrates how definitely disease of the lungs decreases vital capacity and also how the reduced capacity increases with the healing of the disease.

A young woman complained of the recent development of symptoms that suggested pulmonary tuberculosis. An examination in May, 1921, revealed definite evidence of slight disease involving the apices of both lungs. At that time her vital capacity was 2400 cc. A record made in September, 1919, showed that the examination had then disclosed no evidence of pulmonary disease. At that time her vital capacity was 2686 cc. The actual loss in capacity of approximately 300 cc. was of definite significance in this case.

A young man, complaining of pain in the chest in March, 1921, was found to have a very slight pulmonary lesion in addition to acute pleurisy at the base of one lung. His vital capacity was 3550 cc. A record made in September, 1920, showed his lungs to be entirely negative. At that time his lung capacity was 4030 cc. After prolonged treatment in both sanatorium and home his signs entirely disappeared, and his lung capacity was found to be 4000 cc. in May, 1924.

A young man reported for examination because of a recent exposure to tuberculosis. Very definite involvement of a moderately advanced nature was found in both upper lobes in April, 1921. The diagnosis was confirmed by the presence of tubercle bacilli in the sputum. His vital capacity was found to be 3400 cc. (fig. 4). A record made in September, 1919, showed his lungs to be clear at that time. Then his vital capacity was 3670 cc. It was impossible to convince this patient that strict and prolonged treatment was necessary in his case. He continued doing some work and finally decided to go West. He did this, but one year later (April, 1922), on his return, an examination revealed extension of his tuberculosis. At this time his lung capacity was 3100 cc. He then decided to go to a sanatorium but died in less than one year. This case illustrates the value of the vital-capacity test, not only in diagnosis but also in following the progress of the disease.

A young man reported for examination in May, 1921, because of pain in the chest, fever and loss of weight. An examination revealed pulmonary tuberculosis, which proved to be acute and involved the left upper lobe. His vital capacity was 4400 cc. An examination had been made in October, 1917, at which time his chest showed no evidence of disease. At that time his vital capacity was 4650 cc.

A man of about thirty years had recently lost weight. He also complained of fever and malaise. After having a frank hemoptysis he requested an examination of the chest in December, 1920. This revealed pulmonary tuberculosis, involving the middle and lower lobes of the right lung. In May, 1921, his vital capacity was 2400 cc. However, artificial pneumothorax had been begun before this reading was taken. A record of an examination made in September, 1912, while he was a student, showed no evidence of thoracic disease. At that time his vital capacity was 4635 cc.

A young man who had worked his way through college developed symptoms which led him to suspect tuberculosis a few weeks before graduation. An examination made in May, 1924, revealed unmistakable tuberculosis involving the left upper lobe. His vital capacity was found to be 3700 cc. He had been examined in October, 1917, when his chest was reported entirely negative. At that time his vital capacity was 4587 cc.

A pharmacist became acutely ill and was told that she had influenza. After the symptoms failed to disappear she was examined in June, 1923, for pulmonary tuberculosis, which was found to involve the left upper lobe. Her vital capacity was 2300 cc. I had examined this patient and requested stereoscopic plates in April, 1921, at which time no evidence of pulmonary disease was evident. She then had no complaints but had recently been exposed to

tuberculosis. Her vital capacity was 3000 cc. With the development of tuberculosis her vital capacity had decreased 700 cc.

A minister reported for an examination of the lungs which revealed a pleural effusion on the right side. He stated that three weeks before he had had pneumonia and since that time had noticed considerable dyspnea. Fluid removed for diagnosis was clear. This patient's vital capacity was 2300 cc. (fig. 5). An examination which I had made eight months before showed no evidence of chest disease, and the vital capacity was 5000 cc. After the second examination, when the vital capacity was so definitely reduced, he was made a complete bed patient. After approximately ten weeks in bed the vital capacity had increased to 2800 cc. In the next week the capacity increased to 2950 cc., the next week to 3050 cc., and the third week to 3275 cc. Two weeks later this patient came in with the complaint that he had contracted a severe cold. The physical signs in his chest had increased and his vital capacity had decreased to 2850 cc. Soon afterward he moved to another city and, although I have had correspondence with his present physician, I have never been able to obtain further lung-capacity readings. This case also illustrates well how the vital capacity is of value not only in diagnosis but also in following the progress of the disease.

A young woman of small stature developed extensive pneumonia. When first taken during the course of this disease in December, 1921, her vital capacity was only 800 cc. In October, 1920, I had examined her when her lungs were clear, as was evidenced by physical and stereoscopic plate examinations. Then her vital capacity was 2000 cc. Since her attack of pneumonia I have examined her on several occasions. Her vital capacity had returned to 1900 cc. in December, 1923.

SUMMARY

1. Observations on several thousand persons have proved that theoretical normal vital-capacity standards are fairly satisfactorily worked out but, on account of individual variations like theoretical normal weight standards, they can never be highly satisfactory. The normal standards which have to date proved most satisfactory are those based on surface area of the body or standing height, the latter being less accurate.

2. Cases are cited to show that the vital capacity test is of tremendous value both in diagnosis and the guidance of treatment when serial readings are made, and particularly when at least one of these readings was taken at a time when the patient was in good health.

3. The vital-capacity test is recommended strongly as a routine procedure in every physical examination.

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A STUDY OF THE CLINICAL FINDINGS AND RING TEST IN 500 CASES EXAMINED FOR TUBERCULOSIS[1,2,3]

J. A. MYERS

Since Larson, Montank and Nelson (1) published the results of their work on the ring test in the diagnosis of tuberculosis a great deal of interest has been aroused in this subject. It is true that the diagnosis of tuberculosis has been much facilitated by the advent of the X-ray, tuberculin, recent advancement in our methods of physical examination, and a better understanding of the significance of certain facts in the patient's history. Yet, when one considers, after all, how crude our methods of examining are; how we are forced by a physical examination to elicit evidence through a wall covering an invisible area far from the outer surface of that wall, and how much density must be present to obstruct the X-ray sufficiently to cast shadows upon the photographic plate, one truly realizes that there is great need for more delicate diagnostic procedures to detect certain cases of early clinical tuberculosis. But more difficult than the detection of a tuberculous lesion may be the determination of activity of such a lesion. It is well known that a tuberculous lesion may become latent and be reactivated at a later time. From the standpoint of the therapeutist it is of utmost importance to be able to determine the reactivation near its beginning. If one is compelled to wait for obvious symptoms of clinical activity the prognosis is definitely clouded when such activity is determined. Moreover, in convalescence all signs and symptoms, as we know them, may be absent for a long time, yet there may be just enough activity of the lesion to contraindicate exercise and work. Therefore, we are badly in need of a test to aid in the detection of beginning tuberculous lesions as well as those only slightly active.

[1] From the Departments of Preventive Medicine and Internal Medicine, University of Minnesota, and the Minneapolis General Hospital.

[2] Presented, in part, before the Medical Staffs of the Lymanhurst School and Hospital for Tuberculous Children, and the Parkview Sanatorium, September 23, 1924.

[3] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

Since the ring test seemed to have very definite possibilities, about one year ago I decided to make a study of cases upon whom this test could be done. In every case the specimen of blood was sent to Dr. Larson and Mr. Montank with no other information than the name of the patient. The test was performed and reported positive or negative. In the meantime the history, physical and X-ray examinations had been made and the results recorded. It then became necessary to compare the results of these clinical studies with the results of the ring test. So far as the clinician is concerned, it is necessary to take for this test only 1 cc. of blood in the same manner as for the Wassermann test.

TABLE 1

304 cases with negative ring tests

1. Clinical findings entirely negative	247
2. Pulmonary tuberculosis demonstrable; nonclinical	10
3. Patients in sanatoria or hospitals when test was made:	
a. Proved to be nontuberculous	3
b. History of tuberculous pleurisy; no evidence of disease	1
c. Old healed tuberculous hip	1
d. Pulmonary tuberculosis demonstrable; nonclinical	4
e. Far-advanced cases near death	6
f. Moderately advanced cases with slight or no symptoms	5
g. Positive ring test on admission; became negative under treatment	1
h. Tuberculous kidney; slight lesion proved by nephrectomy	1
4. Patients now under close observation:	
a. Apparently arrested (post-sanatorium)	4
b. Apparently arrested (home treatment)	2
c. Tuberculous pleurisy several months ago	1
d. Tuberculous kidney removed one year ago	1
e. Tubercle bacilli in sputum; good working capacity	2
5. Ring test positive on first examination; later negative:	
a. Acute bronchitis	14
b. Pulmonary tuberculosis; test negative after prolonged treatment	1
Total number of cases	304

In this paper 500 cases are reported. This group consists of persons taken from private practice, the University of Minnesota Students' Health Service, and the Parkview Sanatorium. The ring test was negative in 304 and positive in 196 cases. Among the 304 negative cases (table 1) 247 were also entirely negative to all other phases of the examination. In 10 of the remaining cases demonstrable nonclinical tuberculosis was revealed. All of these cases have full working capacity and, according to their histories, have never had clinical tuberculosis. Twenty-two of the remaining cases were in a sanatorium at the time the

ring test was made. These constitute such an interesting group that a few of them deserve citation. Three of them have proved to be non-tuberculous, and one had chronic osteomyelitis of a tuberculous nature. Another was sent in for pulmonary tuberculosis which she did not have. Another very interesting case was that of a man who was referred to the sanatorium for tuberculosis therapy. After careful and sufficiently long observation and study, we discharged this patient with a diagnosis of bronchial asthma. Another patient was sent because of a history of tuberculous pleurisy. Observation in the sanatorium revealed no evidence of clinical tuberculosis. A woman was sent in because of a tuberculous hip which proved to be an old healed lesion. Two other women and one man with minimal lesions at one apex never presented any symptoms or other evidence of clinical tuberculosis while in the sanatorium. Their sputum examinations were persistently negative for tubercle bacilli. There were 6 cases with unmistakable and far-advanced tuberculosis in this group of sanatorium patients with negative ring tests. In fact, two of these patients have already died, and the others are apparently near death. Montank calls attention to negative reactions in far-advanced cases. It would seem that the cause may be explained as in far-advanced and terminal cases with negative tuberculin reactions. Five other cases, classified as moderately advanced, with moderate symptoms and with positive sputum, presented negative ring tests. Unfortunately, it has not been possible to repeat the test in these cases. Another patient with positive ring test on admission to the sanatorium presented a negative test after more than a year of treatment.

Another interesting group consists of 10 of the remaining cases now under observation at home. Four of these have histories of sanatorium treatment over long periods of time, but were all discharged as apparently arrested and now have good working capacity. In only one of these patients is there any record of positive sputum while in the sanatorium. The others were negative on many examinations. One hemoptysis case with bacilli in the sputum was treated at home over a long period of time. He has now been restored to a full working capacity. Although the ring test was positive while he had clinical activity, it is at present negative. Another patient who had not been in good health for some time lost an infant nine months old of tuberculous meningitis. The pediatrician in charge of the infant's case advised the father to be examined. The examination revealed tuberculosis of one upper lobe with tubercle bacilli in the sputum. After a long period of treatment at home

this patient was able to carry on his usual work. No ring test was taken while his disease was clinically active, but a recent test was negative.

In one case of tuberculous pleurisy, in which bacilli were demonstrated in the pleural fluid a few months previously but which was on rigid treatment for a considerable period of time, the ring test was found to be negative. This patient had presented no clinical signs or symptoms since the original attack. He had full working capacity at the time the test was made. Another patient had a tuberculous kidney removed more than a year before the ring test was taken. He now has a demonstrable nonclinical lesion in the apex of one lung but has been restored to full working capacity. Nevertheless, he remains under close observation. A patient with a very definite fibroid process in the upper lobe of one lung and with tubercle bacilli in the sputum gave a negative ring test. He presented no symptoms except slight cough and expectoration. His working capacity was excellent. A woman with a similar condition also belonged to this class. Both were instructed regarding preventive measures and advised to keep under close medical observation. Physicians doing tuberculosis work know that some cases with positive sputum have no clinical activity and are capable of doing much work. In this connection I may quote Lawrason Brown:

> The occurrence of tubercle bacilli in the sputum indicates pathological activity possibly in 90 per cent of all cases, and the presence of elastic tissue in 100 per cent of all cases. No other laboratory test is of any value in ordinary practice in the determination of activity, and all of us have known of many cases of pulmonary tuberculosis which for years have shown continuously or intermittently tubercle bacilli in the sputum, and yet have manifested no signs of clinical activity.

Of the remaining 15 cases 14 on first examination had clinical findings of acute bronchitis. The ring test at that time was positive in each case. After several weeks to a few months had elapsed in each case and all signs and symptoms had disappeared, the ring test was found to be negative. From this small group of cases it would appear that acute bronchitis is capable of producing a positive ring test. In fact Montank (2) (3) says, "It was also found that serums from apparently normal persons suffering from acute colds gave positive reactions for a few days when the cold was at its height." However, mention should be made of the possibility of old latent tuberculous lesions becoming sufficiently reactivated to produce positive reactions when the body resistance is attacked. The last case was one of definite pulmonary tuberculosis which after prolonged treatment presented a negative ring test.

The group of 196 cases (table 2) with positive ring tests consisted of 149 cases with definite pulmonary tuberculosis, one with tuberculosis of the salivary glands, two with tuberculosis of the cervical lymph nodes, two with tuberculous pleurisy, 30 questionable cases and 12 with all clinical findings negative. Ninety-nine of the cases of pulmonary tuberculosis had positive sputum, 45 had negative sputum and in 3 cases sputum was not submitted for examination. Two patients with definite pulmonary lesions well under control presented negative ring tests. Under heavy strain they began to develop symptoms of active tuberculosis. In addition to other symptoms one had a small hemorrhage. In

TABLE 2

196 cases with positive ring tests

1. Pulmonary tuberculosis:	
a. Tubercle bacilli found in sputum	99
b. Tubercle bacilli not found in sputum	45
c. Sputum not examined	3
d. Negative ring test; later became positive	2
2. Nonpulmonary tuberculosis:	
a. Tuberculosis of salivary glands	1
b. Tuberculosis of cervical lymph nodes	2
c. Tuberculous pleurisy	2
3. Questionable cases:	
a. Chronic bronchitis and asthma	8
b. Acute bronchitis	8
c. Histories of definite and prolonged exposures	4
d. Extensive thickening of the pleura	2
e. Low vital capacity	1
f. Malaise and occasional night-sweats	1
g. Chronic osteomyelitis; etiology not definite	1
h. Pneumonia not completely resolved after four months	2
i. Old fibroid process, one apex; suspicious symptoms	1
j. Tuberculous kidney removed more than one year ago	1
k. Previous diagnosis of vicarious menstruation	1
4. No evidence of tuberculosis on physical and X-ray examination	12
Total number of cases	196

both cases the ring test became positive. Several months later, after one of these cases had responded to treatment, the test again became negative.

The two cases of cervical adenitis were very definite cases, although biopsy was not performed. Tubercle bacilli were recovered from the pleural fluid in both cases of tuberculous pleurisy. Biopsy confirmed the diagnosis in the case with tuberculous salivary glands.

Of the 30 questionable cases, 8 have histories of chronic bronchitis, some with occasional asthmatic attacks extending over several years. Eight others had acute bronchitis at the time of the examination. It is possible that a test, after all evidence of bronchitis had disappeared,

might have placed them in the group with positive ring reaction cases which later became negative. Four cases with no demonstrable lesions gave histories of very definite and prolonged exposures. Two patients had extensive thickening of the pleura, which made it impossible to study carefully the lung parenchyma. No tubercle bacilli were found in the sputum. One patient reported because he had been told at several different times that his lung capacity was considerably below the normal. No evidence of tuberculosis could be obtained from the clinical examinations. Another young man in this group reported because he had recently experienced malaise and was having occasional night-sweats. In this case the clinical examination was also negative. One woman of nearly forty years complained of pain in the chest. She had suffered from chronic osteomyelitis for many years although the last sinus had recently completely healed. She stated that she had been told by one physician that she had tuberculous osteomyelitis. This physician, an eminent orthopedist, had died only a few years before the examination and I was never able to learn of the evidence which he possessed. At any rate, no pathological changes were detected in the chest.

Two patients gave histories of having had pneumonia a few months before their examination for tuberculosis. The convalescence was much prolonged; so much so, indeed, as to arouse the suspicion of their friends. There were physical signs and X-ray findings over the areas of the old pneumonia which apparently were due to unresolved conditions. Tubercle bacilli have not been demonstrated, however, and these patients are being observed at rather frequent intervals. An ex-service man with a fibroid process in one apex, and doing unusually heavy work, reported for examination. He had developed slight but suspicious symptoms in the past few weeks. His apical lesion could easily be detected but no râles could be elicited. He has been placed under close observation. In a young woman, who more than a year ago had a positive ring test, no pulmonary lesion could be detected, but later she had a tuberculous kidney removed. Since that time she had developed an arthritis which her orthopedist believes to be nontuberculous. Although her chest is apparently normal, the ring test remains strongly positive. At the present time she is being studied for tuberculous lesions in other parts of the body. The only remaining case in this group of questionable cases is that of a young woman who gave a history of slight hemoptysis accompanying each menstrual period. No evidence of tuberculosis was obtained from the examination.

In the entire group of 196 cases with positive ring tests there were 12 in whom no evidence of tuberculosis was found. When one considers that tuberculous lesions may develop in any part of the body, and how difficult it is to detect small lesions although slightly active, one must consider the possibility of these cases having such lesions that have not been detected. Some of these cases gave histories of definite and prolonged exposures. One patient with such history of exposure had been examined by several leading internists in Minneapolis and St. Paul, all of whom reported no evidence of tuberculosis. The roentgenologist reported "normal chest." The ring test was positive at that time. Six months later she had a frank hemorrhage, and she is now being treated in a sanatorium for tuberculosis.

SUMMARY

1. Among 500 cases examined for tuberculosis the ring test was negative in 304 and positive in 196.

2. Of the 304 negative ring-test cases the clinical findings, as far as active tuberculosis is concerned, were in complete agreement with the test in 276. Six of the remaining cases had far-advanced disease and were apparently near death. Fourteen other cases with positive ring tests in the presence of acute bronchitis became negative after the bronchitis disappeared. Five other patients with tubercle bacilli in the sputum had good working capacity and were free from symptoms. In only the following 6 cases is there no explanation to offer for the apparent discrepancy. One of these is a case with a tuberculous kidney confirmed by pathological examination after nephrectomy. The remaining five cases have moderately advanced disease with slight or no symptoms.

3. Of the 196 positive ring-test cases the clinical findings were in complete agreement with the test in 154. In 30 of the remaining cases not enough evidence could be gathered to make a definite diagnosis of active tuberculosis yet in nearly all of these cases there was enough evidence to arouse suspicion and warrant further observation and study. In the remaining 12 cases the clinical examination was entirely negative.

I am deeply indebted to Dr. Larson and Mr. Montank, of the Department of Bacteriology and Immunology of the University of Minnesota, who very kindly performed all the ring tests for this study.

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AGGLUTINATION REACTIONS OF THE PARATYPHOID-DYSENTERY GROUP IN TUBERCULOSIS [1]

THOMAS G. HULL, KIRBY HENKES AND HUGH CASSIDAY

In a previous paper (1) attention was drawn by the authors to the phenomenon already noted by other investigators that individuals in various stages of tuberculosis very often gave a partial agglutination reaction with the typhoid bacillus. Continuing the study further (2) it was found that the Flexner dysentery bacillus gave even more marked reactions than the typhoid bacillus in such instances. The present paper is published for the purpose of recording reactions obtained with blood from tuberculosis patients carefully classified as to the stage of the disease, and with blood serum and with other body fluids.

Specimens of blood were drawn from 30 patients at a sanatorium where they were well classified. A few drops of blood were allowed to dry on parchment paper and then sent to the laboratory. For the test the blood was moistened with distilled water to equal a dilution of about 1 to 20 and mixed with equal parts of a saline suspension of *B. dysenteriae Flexner* (slant agar culture grown over night at room temperature). The incubation period was one hour at body temperature.

The results, summarized in table 1, would seem to indicate that the stage of the disease has little effect upon the agglutination reaction. About 36 per cent of the cases gave a partial or complete reaction, the higher rates occurring among the moderately advanced cases. The total number is too small from which to draw definite conclusions, however.

It has been shown that both the typhoid bacillus and the Flexner dysentery bacillus give partial or complete agglutination reactions with the blood serum of certain individuals. It was desirable to determine what other members of the gram-negative-bacillus group would give similar reactions. Accordingly, tests were set up on specimens of blood submitted for the tuberculosis-fixation test. The histories of these patients were unavailable; but this is of less importance, since this study was made primarily for comparative purposes of agglutination reactions

[1] From the Division of Laboratories, Illinois Department of Public Health, Springfield, Illinois.

with the typhoid and Flexner microörganisms and the other members of the group. Clear serum was diluted 1 to 20, and a drop of this mixed with a drop of culture (twenty-four-hour slant agar cultures grown at room temperature, and washed off with physiological salt solution).

TABLE 1

Summary of results of agglutination reactions of B. dysenteriae Flexner by blood serum of tuberculous persons

	TOTAL	POSITIVE	PARTIAL	NEGATIVE
Incipient	5	0	1	4
Moderately advanced A.	8	1	3	4
Far advanced A.	3	0	1	2
Moderately advanced B.	4	0	2	2
Far advanced B.	10	1	2	7
	30	2	9	19

TABLE 2

Results of agglutination tests of various members of the typhoid-dysentery group with blood serum of persons suspected of having tuberculosis

	TOTAL	POSITIVE	PARTIAL	NEGATIVE
Typhosus	24	0	5	19
Paratyphoid A	22	0	0	22
Paratyphoid B	22	1	9	12
Flexner	24	10	9	5
Hiss	22	2	8	14
Shiga	13	5	5	3
Pullorum	24	0	0	24
Abortus equii	21	14	1	6
Abortus Bang	22	1	3	18
Melitensis	9	0	3	6
Suipestifer	22	5	0	17
Pestis cavei	22	0	13	9
Alcaligenes	13	0	4	9
Enteriditis	13	9	3	1
Anatum	22	2	6	14

From table 2 it is apparent that most of the bacteria tested gave reactions similar to those of the Flexner bacillus, though less marked. The only two exceptions were *B. paratyphosus A* and *Bact. pullorum* which were uniformly negative. Some of the microörganisms, notably *Bact. abortum equii* and *B. enteriditis*, gave a higher percentage of positive reactions than B. dysenteriae Flexner.

It is to be noted that different blood serums did not agglutinate the various cultures consistently. As an example, in the tests for April 17 serum 1 agglutinated the Flexner bacillus but did not agglutinate *abortus equii* while with serum 6 the reverse was true.

The macroscopic agglutination test was used with a dilution of 1 to 40, with an incubation period of 60 minutes in the water-bath at 37°C., and over night in the ice box. Of 6 serums tested with 10 microörganisms, all tests gave a partial agglutination with *B. typhosus* and similar but stronger reactions with the Flexner bacillus and *abortus equii*, while

TABLE 3

Summary of results of absorption tests

	FLEXNER	ABORTUS EQUII	PESTIS CAVEI	ANATUM	ENTERIDITIS	TOTAL
Agglutinins absorbed by:						
Flexner:						
Total tests		7	1	2	3	13
Entirely absorbed for		0	0	1	1	2
Abortus equii:						
Total tests	5		1	1	2	9
Entirely absorbed for	2		1	1	0	4
Pestis cavei:						
Total tests	1	1		1	1	4
Entirely absorbed for	0	0		1	0	1
Anatum:						
Total tests	2	1	1		1	5
Entirely absorbed for	2	0	0		0	2
Enteriditis:						
Total tests	3	3	1	1		8
Entirely absorbed for	2	0	1	1		4

abortus Bang gave partial reactions in 5 out of 6. The other 6 microorganisms were uniformly negative (paratyphoid A and B, dysentery Hiss, pullorum, melitensis and suipestifer).

Absorption tests were made with five microörganisms, namely, *B. dysenteriae Flexner*, *B. abortus equii*, *B. pestis cavei*, *B. anatum* and *B. enteriditis*, on routine blood samples sent in for the tuberculosis-fixation test.

Thirty-nine tests were made on 8 different serums. Summarizing the results in table 3, agglutinins were completely absorbed in 13 instances

(33 per cent). The Flexner bacillus completely absorbed agglutinins for the other four microörganisms in only 2 out of 13 cases. *Abortus equii* and *enteriditis* each showed complete absorption in about one-half of the instances. Tests with *pestis cavei* and *anatum* were less in number.

From these few tests it would seem that positive or partial agglutination tests obtained in instances such as described in this paper are non-specific. The fact that in a few instances one microörganism absorbs the agglutinins for another might possibly suggest specific infections in those instances, though the data here assembled are too meagre to draw any conclusions from them.

AGGLUTINATION TESTS WITH OTHER BODY FLUIDS

Urine was collected from 15 patients with active advanced tuberculosis in a hospital. Agglutination tests were set up by the microscopic method with a 24-hour agar culture of *B. dysenteriae Flexner* and urine in dilutions of 1 to 2, 1 to 40 and 1 to 80 (microscopic method, 1 hour incubation). Thirteen specimens of urine gave uniformly negative agglutination reactions, while two were positive (complete agglutination in the lowest dilution and negative in the higher dilution). Upon searching the histories of the patients it was found that the 13 patients giving negative reactions all had pulmonary infections, while those 2 giving positive reactions had intestinal infections.

In addition to the above tests, 8 specimens of urine were collected from clinic cases which had been under treatment for a considerable length of time and which were showing improvement. Agglutination tests were set up as above, all of which were uniformly negative. As far as could be determined, no intestinal infections were present in the clinic group.

Several agglutination tests with the Flexner microörganism were made with whey from cow's milk. After removing the butter-fat, the skimmed milk was mixed with a small amount of rennet and allowed to stand till a firm curd had collected. By cutting around the edges clear whey was easily obtained. Various dilutions of whey were incubated with the Flexner bacillus 1 hour at 37°C. and examined microscopically.

Fourteen specimens of mixed market milk were collected at the receiving vats of several dairies. Dilutions at first were run 1 to 2, 1 to 10 and 1 to 20, but they were later cut down to 1 to 2, 1 to 4 and 1 to 8. Seven samples were entirely negative, while 5 gave complete agglutination in

the lowest dilution, and 2 gave partial reactions. The sources of the various specimens were not investigated as to whether the cows were free from tuberculosis or not.

From the extent of tuberculosis among dairy cattle, however, probably in most instances there were some tuberculous animals in each herd.

Twelve cows from a tuberculin-tested herd, all supposed to be free from tuberculosis, were milked into separate containers on two successive days. Tests were set up as previously. On the first day the whey from 2 animals gave complete agglutination, 5 partial and 5 negative. The next day the totals were about the same, but it is to be noted that specimens did not check in every instance; there was a partial reaction one day and negative the next, or vice-versa. A complete reaction one day was in no instance negative the other day.

COMMENT

A considerable number of investigators (3) have pointed out that the Widal test might be positive in tuberculosis. Incipient tuberculosis was supposed to give a higher percentage of positive tests than the more advanced cases. From the small number of well-classified cases available for this study it could not be shown that the stage of the disease was important.

Another group of workers (4) has investigated very carefully the cases giving apparently nonspecific Widal tests, and has found in many instances that typhoid infection actually did exist. Chesley and Wade made tests on 1017 tuberculous individuals, obtaining 35 partial or complete Widal reactions. The feces and urine of 14 of these were cultured, with the result that typhoid bacilli were isolated from 7 cases. Several of the other cases gave a previous history of typhoid fever. It would seem therefore that, in many instances in which a positive Widal test is obtained in tuberculosis, the real cause is a previous attack of typhoid fever, leaving the individual in a carrier state. The results of the present investigations, however, do not substantiate this hypothesis. Not only are positive agglutination reactions obtained with the typhoid bacillus but with 12 other microörganisms of the gram-negative group. It would appear that the reaction is entirely nonspecific.

Several investigators (5) have found that a considerable percentage of the population give positive agglutination reactions with *Bacillus abortus Bang*, some putting the figure as high as 25 per cent. In the results

here reported this is about the figure obtained. It is to be noted, however, that *B. abortus equii*, as well as many other microörganisms gave a much higher percentage. Very probably a nonspecific reaction with *B. abortus Bang* must also be guarded against.

Positive Widal reactions have from time to time been reported in various conditions (6). Among these are pneumonia, miliary tuberculosis, Weil's disease and sepsis. Cases of chronic cholecystitis (7) often give positive Widal reactions, but these may be due to typhoid infections of the gall-baldder. The writer recently obtained strongly positive Widal reactions on two different days in a well-developed case of measles. It was impossible to obtain the previous typhoid history on the case, however.

Other body fluids, such as urine and milk, might be expected to agglutinate the group of microörganisms used in this study, when they were so easily agglutinated with blood serum. It is interesting to note that the only tuberculous patients whose urine gave positive reactions were those with intestinal lesions. The question arises whether superimposed upon the intestinal tuberculosis there was not some other infection.

The fact that both mixed market milk and milk from a supposedly tuberculosis-free herd of cows gave reactions not unlike those obtained with blood serum and urine of persons would lend further weight to the probability that the reactions obtained in this study are nonspecific and are caused neither by typhoid nor tuberculous infections.

CONCLUSIONS

1. Certain members of the paratyphoid dysentery group of intestinal microörganisms were found to agglutinate readily with blood serum and urine from persons and milk whey from cows.

2. From studies made on patients in a tuberculosis sanatorium it is not apparent that the stage of tuberculosis has any effect on the agglutination test.

3. Urine from 23 tuberculosis patients agglutinated the Flexner dysentery bacillus in only two instances in which intestinal tuberculosis was present.

4. Whey from both mixed market milk and from nontuberculous cows agglutinated in many instances the Flexner dysentery bacillus.

5. From the results of absorption tests it is probable that the agglutination reactions obtained in this study are due to no specific infection, but are common to the paratyphoid-dysentery group of microörganisms.

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HELIOTHERAPY IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

R. H. McCUTCHEON

In this paper I shall use the term *heliotherapy* only in its stricter sense, as referring to treatment by the direct rays of the sun. No attempt will be made to discuss the physical properties of light or to explain the physiological action on the human body; and our experience has been too limited to speak in a didactic manner or to lay down any set rules to govern the use of the sun-treatment in pulmonary cases.

For several years, at the State sanatoria at Cresson and Mont Alto, it has been the custom to dress the children patients in one-piece play suits during the spring, summer and autumn months, exposing as much of the bodies as possible. The good effect of this partial exposure is difficult to measure, but it was sufficient to encourage us to make a definite and systematic use of the sun in treating our adult pulmonary cases at Mont Alto.

During the summer and fall of 1922, 100 patients of the Veterans' Hospital Unit of the sanatorium were placed on sun-treatment as an experiment. The medical supervision of the treatment was good, but many of the men insisted on walking about the grounds stripped to the waist after treatment and several cases of severe sunburn and sharp rises in temperature resulted. The difficulty in rigidly enforcing the requirement of sun-treatment on men so recently discharged from the military service discouraged the Staff, and the treatment was discontinued before it was possible to determine its value. The treatment was given on the large roof of the soldiers' recreation room and cots were furnished for the purpose. The breakage of cots amounted to almost 100 per cent in a month's time. No heliotherapy was attempted the following year, but preparations were made to institute it in 1924.

During the spring of 1924, two already existing cure-pavilions were altered by removing the roofs, and building five-foot partitions around

[1] From the Pennsylvania State Sanatorium for Tuberculosis, South Mountain, Franklin County, Pennsylvania.

[2] Read before the Pennsylvania Tuberculosis Society, Pittsburgh, Pennsylvania, January 21, 1925.

them to exclude the wind and insure privacy. One hundred wooden benches were constructed for the patients to lie on, six feet long, two feet wide, nine inches high at one end and seven inches high at the other. The pavilion assigned for the treatment of men was twice the size of the women's pavilion, and held 65 of these benches arranged in rows across and around the sides of the pavilion, while the women's pavilion held 35 benches. Since the pavilions and benches constituted all the necessary equipment, it can be seen that the expense was very small and the cost per capita treated was negligible. The equipment of the patient consisted of a straw, linen or paper hat, dark glasses, loin-cloth, bathrobe, slippers and blanket to lie on. The patient was required to furnish his own equipment except the loin-cloth, which was made at the institution, and the blanket.

SELECTION OF PATIENTS

The selection of the patients to be treated was no easy matter, and in order that it should not be done in a haphazard fashion, a definite plan was devised as follows: From our ambulant cases we selected those who had spent more than four months in the sanatorium, and who had become stationary and still showed clinical evidence of activity, regardless of the stage of their disease. From the recent admissions, cases were selected with a more or less favorable prognosis, and with no, slight or a moderate degree of toxemia. Lastly, we selected cases with various complications, tuberculous and otherwise, some of whom were semi-bed cases and many with a moderate degree of toxemia. In all, 166 cases were assigned to heliotherapy during the summer, but only 105 continued the treatment from three to five months. Sixty-one cases were permitted to discontinue the treatment for purpose of discharge or because of taking employment in the sanatorium, and a few chronic "kickers" were allowed to stop before their bad influence on other patients was felt.

All of the cases were able to walk to the sun-pavilions, and all were selected only after careful study. All had been accustomed to taking the cure on the open-air pavilions for at least two weeks and the majority had spent more than 60 days in the sanatorium. Physically, they were fairly representative of our camp cases who keep their cottages clean and walk to their meals, but who are required to rest in bed or in cure-chairs the greater part of the day.

In choosing the time of day to give the sun-treatment it was desired to follow as closely as possible the advice of Rollier, and use the early morning and late afternoon hours. However, the months of May and June were exceptionally cool, and May was so rainy that no treatment could be given. The early morning and late afternoon hours could not be used without interfering too much with the established routine of the institution and would have necessitated changing the meal hours. On account of this and the continued cool weather it was decided to give the treatment to the men from 9:00 to 11:00 A.M., and to the women in two periods, because of the small size of their pavilion, from 8:30 to 10:30 A.M. and from 1:30 to 3:30 P.M. This latter time was moved up thirty minutes during September and October when the weather again became cool.

It was with some trepidation that these hours were selected, for they were not in accord with the teachings of Rollier. To guard against any possible ill effects from excessive exposure of heat-stroke, a physician was in attendance at the men's pavilion and a nurse at the women's pavilion. It is interesting to note that with only a few exceptions to be mentioned later there was a total absence of unfavorable symptoms attributable to the intensity of the sun's rays.

TECHNIQUE

The technique of administering sun treatment was that used by Rollier, of gradual exposure of the body beginning with the feet and exposing the chest last.

First day: The feet and ankles are exposed 5 minutes, the rest of the body being covered. This exposure may be repeated three times during the day.

Second day: Feet and ankles are exposed 10 minutes, and legs to knees 5 minutes. This exposure may be repeated twice during the day.

Third day: Feet and ankles are exposed 15 minutes, legs to knees 10 minutes, thighs to hips 5 minutes.

Fourth day: Feet and ankles are exposed 20 minutes, legs to knees 15 minutes, thighs to hips 10 minutes, hips to lower ribs 5 minutes.

Fifth day: The exposure of each part is increased by 5 minutes to front and back, and the chest is exposed 5 minutes, front and back.

Sixth to sixteenth day: From the sixth to the sixteenth day the exposure to each part is increased, 5 minutes daily, until each part is receiving a maximum of 60 minutes' exposure, when no further increase is made. By the sixteenth day the whole body is being exposed for one hour, it taking two hours for the complete treatment. On the very hot, close days, the treatment was

shortened to one-hour periods and the patient turned every 15 minutes. On cooler days the treatment was lengthened to 3 hours. Except on rainy days the treatment was carried on whether the sun shone or not.

RESULTS OF TREATMENT

In determining the reaction of patients under the various headings to follow, only those showing a marked change for the better or worse were so recorded. Where only a minor change took place it was recorded as *no change*, or *same*.

Of the 105 cases who kept up the treatment during the summer there were 54 men and 51 women who were classified as follows: incipient, 5; moderately advanced, 45; and far advanced, 55. Of these, 63 had sputa positive for tubercle bacilli and 42 were negative. There were 60 cases who showed a moderate degree of toxemia and one case a rather severe toxemia.

The various headings under which our *Results of Treatment* have been grouped are as follows:

Physical signs	Hemorrhage or streaked sputum
Cough	Temperature and pulse
Expectoration	Susceptibility to colds
Sleep	Nervous and psychic reaction
Appetite	Complications
Weight	Positive and negative sputum cases
	General considerations

Physical signs: Examination of the lungs of these 105 cases before and after treatment by the sun, upon comparison, showed that in 48 per cent, or 50 cases, the lung moisture was markedly decreased, while 2 per cent, or 2 cases, showed definite progression. One of these latter cases had a complicating tuberculous laryngitis and the other developed a hemorrhage after a brawl with a visitor. Fifty per cent, or 53 cases, showed only slight or no improvement in physical signs. In 100 per cent of the incipient cases, 60 per cent of the moderately advanced cases and 32 per cent of the far-advanced cases, the lung moisture was decreased.

Cough: The symptoms, cough and expectoration have been separated, because it was discovered that a hacking nonproductive cough often disappeared, while in other cases the cough remained about the same but the total amount of expectoration increased or decreased. In 58 per cent, or 61 cases, the cough was entirely absent or markedly

TABLE 1

Results of heliotherapy in 105 cases (comparison of cases at beginning and end of sun-treatment)

For lack of space only cases showing marked improvement or the opposite are shown here.

STAGE OF DISEASE	NUMBER OF CASES	PHYSICAL SIGNS		COUGH		EXPECTORATION		SLEEP		APPETITE		WEIGHT*	
		Decrease	Increase	Decrease	Increase	Decrease	Increase†	Better	Worse	Better	Worse	Gained	Lost
		per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent
Incipient A	5	5–100	0	4–80	0	3–60	1–20	3–60	0	4–80	1–20	5–100	0
Moderately advanced A	21	10–47	0	14–67	0	12–57	4–19	6–28	1–5	8–38	1–5	16–76	4–19
Moderately advanced B	24	17–70	1–4	12–50	5–21	12–50	5–21	9–37	2–8	11–46	1–4	16–66	6–25
Far advanced A	18	6–33	1–5½	12–66	4–22	8–44	6–33	9–50	0	9–50	3–16	8–44	4–22
Far advanced B	36	12–33	0	18–50	6–16	66–44	9–25	6–16	1–2	12–33	3–8	16–44	10–27
Far advanced C	1	0	0	1–100	0	1–100	0	0	0	0	0	0	1–100
Total	105	50–48	2–2	61–58	15–14	52–50	25–24	33–31	4–4	44–38	9–8	61–58	25–24
Positive sputum	63	24–38	2–3	33–52	12–18	26–41	16–25	16–25	3–5	21–33	3–5	28–44	17–27
Negative sputum	42	26–62	0	28–69	3–7	26–62	9–21	17–40	1–2	23–54	1–2	33–78	8–19

* Sixty-one cases gained an average of 5 pounds during heliotherapy.

Twenty-five cases lost an average of 3.8 pounds during heliotherapy.

Cases that gained spent an average of 2.2 months in the sanatorium prior to heliotherapy.

Cases that lost spent an average of 6.7 months in the sanatorium prior to heliotherapy and many were overweight.

† The majority of the 25 cases of increased expectoration claimed that this increase was noticeable only during or immediately after each period of treatment and that there was an actual reduction in the total 24-hour expectoration. As the sputum was not weighed no accurate check of this could be made.

decreased. In 14 per cent, or 15 cases, the cough seemed aggravated, and in 28 per cent, or 29 cases, there was no change.

Expectoration: The usual result of sun-treatment on expectoration was that it became looser, freer, easier to bring up, and increased during and for an hour or two after each period of insolation, but that the amount of expectoration during the rest of the day, and especially in the early morning, was much decreased. In table 1 many of the cases listed as having increased sputum showed this increase, not in the total 24-hour amount, but during and subsequent to each treatment. Fifty per cent, or 52 cases, showed a marked decrease or absence of expectoration after 2 to 4 months of sun-treatment, while 24 per cent, or 25 cases, showed an increase at least after each exposure. In 26 per cent there was no change.

Sleep: Another most favorable effect of the sun was noted in the amount of sleep the patients could take. Thirty-one per cent, or 32 cases, slept better and spent more hours of both day and night sleeping. Many could sleep through their periods of insolation. Four per cent, or 4 cases, stated that they slept less and had more difficulty in going to sleep during heliotherapy and slept better when it was finally discontinued.

Appetite: Naturally, from long exposure to the sun and air, many of the patients reported better appetites, although nearly half of the cases reported good appetites through their entire time of sanatorium treatment. Thirty-eight per cent, or 44 cases, showed appetites much improved, while only 8 per cent, or 9 cases, reported that their appetites were made worse, especially for the meal following immediately after each exposure.

Weight: Our figures in regard to gain and loss of weight during sun-treatment require some explanation. Fifty-eight per cent, or 61 cases, gained an average of 5 pounds from the beginning to the end of their treatment. Twenty-four per cent, or 25 cases, lost an average of 3.8 pounds. The 61 cases that gained weight spent an average of only 2.2 months in the sanatorium prior to starting heliotherapy, and might have made the same gain in the first six months of sanatorium life without heliotherapy. The 25 cases that lost weight spent an average of 6.7 months in the sanatorium prior to heliotherapy, and had already made the usual initial, rapid gain, and some were overweight when the treatment was started. What part the sun played in the gains I cannot say, but the losses seemed most marked in the advanced cases who perspired

freely but showed a favorable reaction otherwise. We did not worry about a loss of from 2 to 10 pounds in cases already up to or above their normal weight, nor did we discontinue the treatment of any case for loss of weight. Weight is regarded so highly by the patients themselves as the best indication of their condition that it was most surprising to find that the majority of the patients who lost weight strenuously objected to discontinuing heliotherapy when this was suggested to them.

Hemorrhage or blood-streaked sputum: Fourteen of our 105 cases had been subject to either hemorrhages or repeated blood-streaked sputum a few months prior to beginning heliotherapy. Of these 14, seven had blood-streaked sputum once or twice during the months of sun-treatment. None of these cases were discontinued for more than two to ten days, and in none could the sun be regarded as the causal factor. Two of the 7 cases developed blood-streaked sputum before the chest had been exposed to the sun at all. Only one case had a definite hemorrhage, and that followed upon a vicious attack by an insane visitor in which he was knocked down. He has had several hemorrhages since that time, although confined to bed, and the sun was not considered as the cause. Probably a smaller percentage of our 105 cases treated by heliotherapy showed this untoward symptom than a like number of cases not treated by heliotherapy under the ordinary sanatorium regimen. I question whether the fears of hemorrhage under sun-treatment are well grounded or based on fact when the treatment is properly dosed and administered.

Temperature and pulse: Practically no change in temperature and pulse was noted under sun-treatment. Our records show that in 9 cases the temperature was reduced and in 24 cases the pulse-rate retarded, while in 6 cases the temperature was elevated and in 10 cases the pulse accelerated. These changes were not marked, and it was felt that they were due to other causes and not to the sun.

Susceptibility to colds: The effect of sun-treatment on the patient's susceptibility to colds was not as important a factor as we were led to expect. Only 13 cases, or 12 per cent, claimed to have been susceptible to colds prior to heliotherapy, and all stated that their colds had not recurred. Four cases, or 4 per cent, reported that exposure to the air and sun caused repeated acute coryzas or made them more susceptible to common colds than before. However, it is only human nature to forget a disagreeable symptom that ceases to appear and to report the symptoms that do occur. In our experience with 200 children in their

play-suits this past summer, we found that colds were entirely absent, and only two prescriptions for colds were written during a period of four months in the Children's Hospital, and they were for recent admissions.

Nervous and psychic reaction: Mention is made in several articles on sun-treatment of unfavorable psychic reactions, rather vague in character and difficult of description. A few of our patients, chiefly women, complained of being made more nervous and restless during their treatments. Headaches were occasionally complained of, but were usually due to failure to properly protect the head, eyes and nape of the neck from the sun's rays. Vertigo or dizziness was present at the menstrual period in a few of the cases. Aside from such nervous symptoms as these, we did not have any case that showed an unfavorable psychic reaction. Reducing the length of the period of insolation relieved the nervous symptoms mentioned, so evidently we were at fault in our dosage in these cases. These symptoms were found almost equally divided among the morning and early afternoon classes.

Results in complicated cases: Twenty-nine of our cases had the following complications which were under treatment at the time of beginning heliotherapy:

Tuberculous laryngitis, incipient and moderately advanced	10
Pleurisy with effusion	2
Tuberculous empyema	1
Rectal fistula	3
Otitis media, purulent	4
Tuberculous arthritis of knee	1
Asthma	1
Tuberculous enteritis	1
Tuberculous epididymitis	1
Syphilis	1
Pustular acne	4

All of the complications showed either marked improvement or cessation of symptoms except the case of syphilis, one case of rectal fistula and the asthma.

The laryngeal cases were receiving two local treatments each week by the water-cooled ultraviolet lamp and two local treatments each week by direct sun-rays. All improved noticeably faster than the laryngeal cases not treated by general sun-exposures.

The two cases of pleurisy with effusion showed a decrease in the amount of fluid after the first month, and it was not necessary to tap

either during the summer months, though both had to be relieved occasionally during the preceding winter and spring.

The case of tuberculous empyema had a profusely discharging sinus, which discharged even more profusely when sun-treatment was initiated but almost dried up during early fall. The discharge has only recently increased again, though it is more than two months since heliotherapy was discontinued.

One case of rectal fistula did not improve under sun-treatment, but the other two were completely healed by two months' insolation.

The 4 cases of otitis media healed entirely, the discharge ceased and they stopped reporting for ear treatments.

The case of tuberculous arthritis of the knee now has almost perfect function, no limp, and the joint appears practically normal. This man gained 40 pounds in weight, and is now able to work five hours daily.

The case of tuberculous enteritis had been treated for six months by exposure to the ultraviolet lamp with only slight improvement. After four weeks of sun-treatment his diarrhea stopped, and stools became formed.

The 4 cases of pustular acne over face and back cleared up entirely. One case which had been treated for several weeks by the ultraviolet lamp with only slow improvement was cured entirely in the first month of sun-treatment.

I regret that the distance of the heliotherapy pavilions from the infirmary did not permit our placing several more cases of tuberculous enteritis on sun-treatment, as the result in the one case treated was so satisfactory. During the coming summer, when the capacity of our women's pavilion is to be doubled, provision will be made for treating many of our complicated cases who are confined to bed.

Positive and negative sputum cases: The prognosis of negative sputum cases with any form of treatment is always better than for cases with positive sputum. Sixty-three of our cases had positive sputum and 42 were negative. On comparing our results of sun-treatment with positive and negative cases, we found that 62 per cent of our negative cases had a marked decrease in lung moisture against 38 per cent of the positive cases. Three per cent of the positive cases and none of the negative cases showed an increase in lung moisture. In 69 per cent of the negative cases and 52 per cent of the positive cases the cough was decreased or entirely absent, while in 7 per cent of the negative cases and 18 per cent of the positive cases the cough increased.

Seventy-eight per cent of the negative cases and 44 per cent of the positive cases gained weight, while 19 per cent of the negative cases and 27 per cent of the positive cases lost weight.

These results were to be expected and do not seem at all significant, nor do they contraindicate the use of heliotherapy in cases with positive sputum. Rather, they demonstrate that the cases with positive sputum may receive improvement under sun-treatment in practically the same ratio as they receive it under ordinary sanatorium regimen.

Some general considerations: Upon questioning our patients on the heliotherapy pavilions toward the end of the summer as to their own conception of the results of sun-treatment, it was found that they were almost unanimously in favor of it because it made their breathing easier and their expectoration freer and easier to bring up, and because they felt stronger, slept and rested better, and had better appetites and were less troubled with hacking coughs. Much regret was expressed that cold weather and sunless days would soon force them to discontinue the hours spent on the pavilions, and many wondered whether the good effects of the treatment would disappear with its discontinuance.

More than two months have elapsed since the pavilions were closed, and I am glad to report that in the majority of cases questioned the good effects have continued. Many are still deeply pigmented, and only a few tell of the return of their former symptoms.

From what we have learned about sun-treatment in pulmonary tuberculosis from others and from our own experience in the past three years, we are willing to recommend it as worthy of a fair and unbiased trial. The good results far overbalance the unfavorable results, and with proper care in selecting the cases, and under medical supervision, few ill effects have been reported. Altitude does not seem to be a requirement, nor is it necessary to continue the treatment through the entire 12 months to obtain results. A suitable porch, pavilion or roof is essential, but fortunately is cheap of construction and much less expensive per patient treated than some forms of artificial light therapy.

No cases of sunburn were noted, and the cases that pigmented best seemed to be the cases that reacted best to the treatment, although a few exceptions were found. All of our 105 cases were well pigmented by the end of the second month, and no failures to pigment were observed.

Heliotherapy cannot be properly carried on unless it is supervised by a physician or nurse, and preferably the former. Variations in

temperature and humidity call for daily changes in dosage, and heliotherapy should be dosed by the physician just as is any other therapeutic agent. The greatest confidence is inspired by the presence of the physician, and a constant watch can be kept for unfavorable symptoms which might necessitate some change from the daily routine. It is the physician who decides that a case is suitable for heliotherapy, and it should be only a physician who administers it.

CONCLUSIONS

1. Heliotherapy is most valuable in pulmonary tuberculosis and its use is to be encouraged.
2. The most remarkable effect on pulmonary cases is the decrease in lung moisture.
3. It is possible in this locality (Pennsylvania) to expose patients at a hotter time of day than is usually advised without unfavorable reactions.
4. The Rollier method of gradual exposure is safe, and, when used, there is little or no danger of hemorrhage.
5. Heliotherapy should be prescribed and supervised by the physician only.

HELIOTHERAPY IN ADVANCED PULMONARY TUBERCULOSIS[1,2]

I. D. BRONFIN

A review of the numerous remedies offered in recent years for the cure of pulmonary tuberculosis or the amelioration of its symptoms leaves one perplexed, for the clinician finds himself literally unable to separate the wheat from the chaff. The early favorable but essentially premature clinical reports on a given method of treatment, followed later by a waning enthusiasm for it or actual proof of its inefficiency, point to the almost insurmountable difficulty in correctly appraising the value of a new therapeutic agent. The task becomes all the more complex when we are mindful of the great susceptibility to psychic influences of the majority of tuberculosis patients. Indeed, some observers have not hesitated to attribute their apparently good results from tuberculin to mere psychic reaction; how much more may that be true of remedies which are still more or less in a state of empiricism?

It is therefore not surprising that heliotherapy, though successfully employed by Rollier since 1903, did not find any ardent advocates in this country until 1913, when Pryor, impressed by Rollier's results, introduced this therapy at the J. N. Adam Memorial Hospital of Perrysburg, New York. This institution has since gained for itself an enviable reputation for the splendid results obtained in cases suffering from various forms of extrapulmonary affections, chiefly bone and joint tuberculosis. Although LoGrasso's (1) report on 634 extrapulmonary cases states that 78 per cent of adults and 18 per cent of children showed evidence of pulmonary involvement, no mention is made as to the effect of solar radiation upon the pulmonary lesion. He (2) has observed, however, that in the treatment of patients with extrapulmonary involvement there has been a tendency for the pulmonary disease to assume a mild course and become quiescent in an unusually short time. Recently the same author (3) has reported favorable results on a group of 49 uncomplicated

[1] From the Sanatorium of the Jewish Consumptives' Relief Society, Sanatorium, Colorado.

[2] Read in abstract at the 54th annual meeting of the Colorado State Medical Society, Denver, Colorado, October 7–9, 1924.

pulmonary cases that had received, on the average, 350 hours of sun-cure. The improvement was evidenced by gain in weight, lessened cough and expectoration, and lymphocytosis, but it seems to us that the period of observation had not been long enough to justify definite conclusions.

While the literature is now fairly replete with convincing proof of the value of heliotherapy for so called surgical tuberculosis, there is considerable paucity as to its value in pulmonary tuberculosis, and opinions are quite contradictory. Kruger (4) treated 30 cases with no unfavorable results, except in two, while Hayek (5), with a material of over two thousand patients observed for four years, could find very little difference in results between the summer months when heliotherapy was practised extensively and the winter months when the sun was not available. Again, Shortle (6) cautions against overenthusiasm for this form of therapy and concludes that the greatest benefit noted from sun exposure was the marked freedom from colds, while Mayer (7) believes that in a few of his selected cases the favorable results can definitely be attributed to the therapeutic properties of the sun-rays. Rollier (8), though 20 per cent of all his cases had active pulmonary lesions, hesitates to draw conclusions, as in his opinion "they can hardly be considered as typical cases of pulmonary tuberculosis." He is nevertheless convinced that heliotherapy would be a useful factor in the treatment of a great majority of properly selected cases, since any "treatment causing improvement in the general health of the patient is our best means of combating pulmonary as well as surgical manifestations."

The problem which seems to us most pressing for a solution is the proper selection of cases, and with it arises the question: What are the indications for treating pulmonary tuberculosis by heliotherapy? Experience has taught us that febrile cases with tachycardia, excessive cough and expectoration, moderate weakness and cachexia, do not as a rule react favorably to solar radiation. Even some subfebrile patients with marked debility rarely do well under insolation. The field thus becomes narrowed down to the low-grade fever patients with little constitutional impairment, or to the typical ambulant cases of chronic phthisis with no symptoms other than the usual amount of cough and expectoration and tubercle bacilli in the sputum. In the latter two types unquestionably good results have been obtained from a strict sanatorium regimen. Therefore, when such patients are placed on heliotherapy and only equally good results are obtained, one is hardly justified in attributing improvement solely to radiation, especially when the rest cure is usually

more strictly observed by the patient under sun treatment than by the one under no special treatment.

In considering this problem, it occurred to us to use controls whenever possible. So far little progress has been made, for it is realized that, after all, there are no two cases alike as regards the type of the pulmonary involvement or the character of the constitutional reaction toward the disease. An attempt has, however, been made, and the observations will constitute the subject of a future report. For the present, the following two cases, briefly cited, will serve to illustrate the difficulty in evaluating a therapeutic procedure:

Case 1: G. P., a married woman, age 27, admitted June 1, 1923. Physical examination disclosed evidence of extensive infiltration involving the upper halves of both lungs and the roentgen plate showed diffuse mottling throughout both pulmonic fields. The laryngoscopic image revealed pear-shaped arytenoids, thickening of the vocal bands and ulcerating granulations in the interarytenoid space. Besides low-grade fever, extreme debility, aphonia and expectoration, there was also a train of gastrointestinal symptoms strongly indicative of enterocolitis. Under a strict regimen of silence and complete bed-rest, aided by the usual hygienic and dietetic measures, improvement gradually followed, and the clinical course has been entirely satisfactory. Her weight, 84 pounds on admission, is now 112 pounds, and the sputum has been negative for five consecutive months. The roentgen plate shows a marked retrogression of the lesion.

Case 2: M. S., male, age 22, admitted Dec. 7, 1922, complaining of excessive cough and expectoration, weakness, dyspnea on slightest exertion, chest pains, anorexia, abdominal cramps and constipation and low-grade-fever. Moderate dysphagia and pains radiating from the sides of the neck toward the ears were additional complaints. Physical examination pointed to a far-advanced active ulcerative lesion, involving the upper halves of both lungs, and the roentgen plate had a striking resemblance to the one obtained in case 1. The clinical course remained unchanged until February 5, 1923, when the patient had a small hemoptysis. Following this, slight improvement was noted, although the temperature continued fluctuating between 99 and 100° F. daily. Systematic heliotherapy was started in April of the same year. The patient became afebrile in July, and the treatment was continued practically without interruption up to June, 1924. There has been a steady gain in weight from 98 pounds to 109 pounds. The sputum, though still positive, has decreased from 4 ounces to one drachm. The last roentgen plate showed a marked clearing of the lesion.

Such and similar observations on a large group of cases under different forms of therapy, including sun radiation, have inspired the undertaking of a critical study of the end-results obtained in our heliotherapy cases, so that an opinion as to the therapeutic value of solarization may be based on facts instead of mere impressions. Although over one hundred cases have been exposed on and off since February, 1921, when this therapy was introduced at the Sanatorium of the Jewish Consumptives' Relief Society, only 50 were selected to serve as a basis for this report. The others have either not been steadily or continuously under treatment

for a sufficiently long period to warrant conclusions, or were not under the author's personal observation and study.

Of the total number, there were 40 men and 10 women. The extent of pulmonary involvement can be seen from the following:

Far advanced active bilateral	40
Far advanced inactive (fibroid)	8
Moderately advanced active	1
Moderately advanced inactive (fibroid)	1

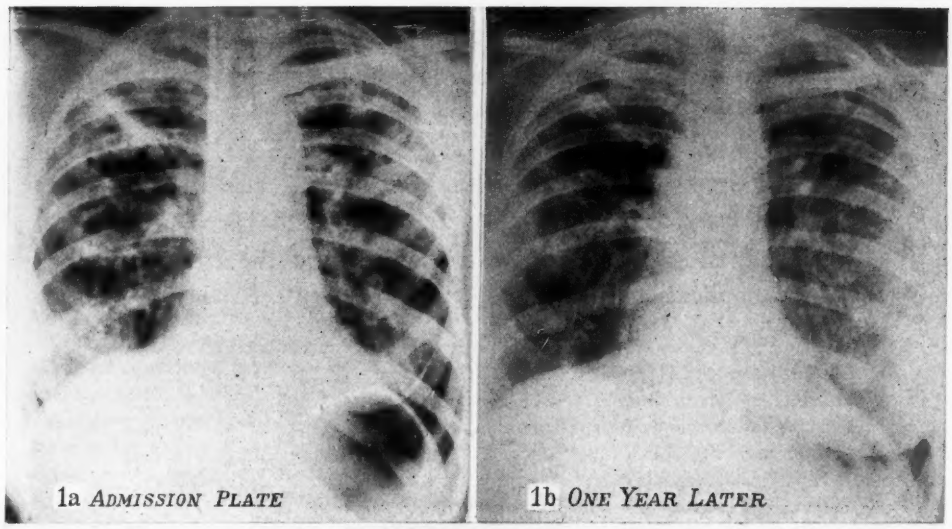
Thirty-two cases presented, prior to beginning the treatment, the following complications:

Subacute tuberculous laryngitis	3
Chronic tuberculous laryngitis	3
Tuberculous enterocolitis	5
Pleural effusion complicating pneumothorax	4
Genitourinary and spinal tuberculosis	1
Tuberculous spondylitis	3
Tuberculous epididymitis, subacute, bilateral	1
Chronic tuberculous laryngitis and epididymitis	1
Chronic tuberculous otitis media	1
Tuberculosis of sternum and left knee joint	1
Rectal fistula	2
Costosternal abscess	1
Multiple infectious arthritis	1
Subacute laryngeal and lingual tuberculosis	1
Tuberculous cystitis	1
Tuberculous nephritis	1

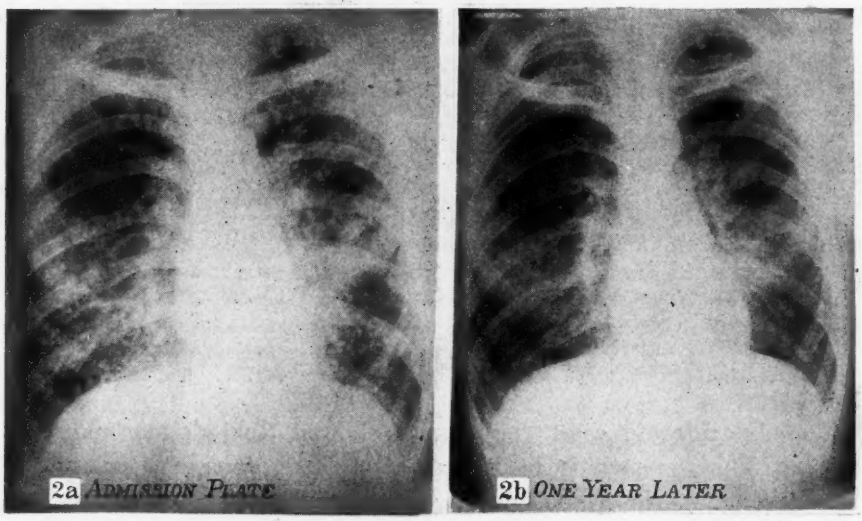
The average period under treatment was a little over a year, and classified as follows:

Two years or longer	6 or 12 per cent
One year or longer	13 or 26 per cent
Six months or longer	23 or 46 per cent
Three months or longer	8 or 16 per cent

In insolating our cases, we closely followed Rollier's systematic or derivative method, which consists in a careful and progressive exposure of the different parts of the body beginning with the lower extremities. Occasionally deviations were made to suit the individual case. Reference to chart 1 will show that the chest was not exposed for many days and not until the rest of the body had begun to show pigmentation. Each patient was given daily air-baths for a week or longer prior to actual solarization. Instructions were issued not to take sun-baths for one hour before and one



CASE 1. UNDER ROUTINE SANATORIUM TREATMENT. NOTE MARKED CLEARING OF MOTTLING IN SECOND PLATE.



CASE 2. UNDER HELIOTHERAPY. NOTE RETROGRESSION OF LESION IN SECOND PLATE.

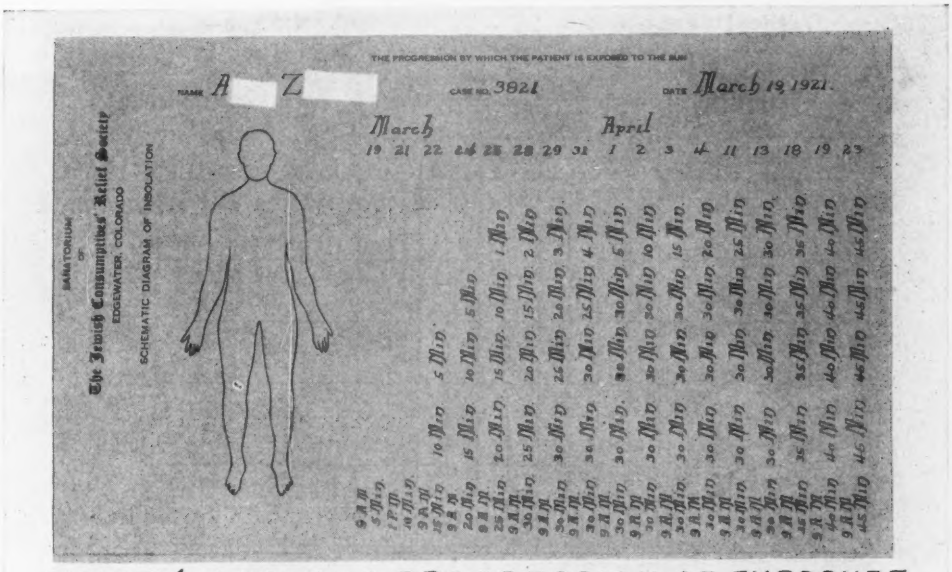

THE PROGRESSION BY WHICH THE PATIENT IS EXPOSED TO THE SUN
NAME A Z
CASE NO. 3821
DATE March 19 1921.
SANATORIUM OF
The Jewish Consumptives' Relief Society
EDGEWATER, COLORADO
SCHEMATIC DIAGRAM OF INSOLATION
March
April
19 21 22 24 25 28 29 31 1 2 3 4 11 13 18 19 23

CHART 1. SHOWING PROGRESSION OF EXPOSURE OF VARIOUS PARTS OF THE BODY TO THE SUN

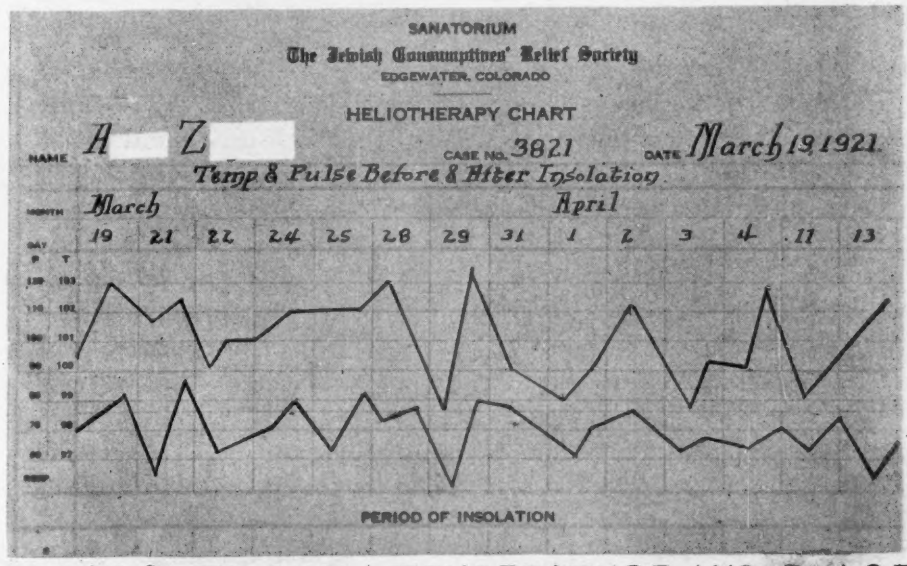

SANATORIUM
The Jewish Consumptives' Relief Society
EDGEWATER, COLORADO
HELIOTHERAPY CHART
NAME A Z
CASE NO. 3821
DATE March 19 1921.
Temp & Pulse Before & After Insolation
MONTH March April
DAY 19 21 22 24 25 28 29 31 1 2 3 4 11 13
P T
PERIOD OF INSOLATION

CHART 2. TO SHOW TEMPERATURE AND PULSE BEFORE AND AFTER INSOLATION

hour after the noon meal, as we learned from experience that exposure during those hours in some way interfered with proper digestion and gave rise to tachycardia. During the hot summer months the treatment was administered in the forenoon, as the afternoon sun frequently caused general depression and occasionally such distressing reactions as rise in temperature, palpitation, dizziness, headache and marked exhaustion. The cool shower or sponge-bath after treatment was encouraged in all cases that had reached an insolation period of one hour or longer. Rest in bed for at least one half-hour after each treatment was insisted upon as a necessary routine measure. A record was kept of the pulse and temperature immediately before and one half-hour after each treatment while resting in bed. Not more than a total of 3 hours' exposure was permitted daily, and in most instances the treatment was divided into morning and afternoon periods. An elevation in temperature of more than one degree or a marked acceleration of the pulse-rate was an indication for decreasing the dosage. The persistence of headache, dizziness, nausea and palpitation, even after the length of exposure was decreased, caused a discontinuance of the treatment until all symptoms subsided. The resumption was gradual as in an initial case. The head and neck were covered by bed awnings and amber glasses afforded protection to the eyes.

ANALYSIS OF RESULTS

In order to determine accurately the progress of each case, the clinical manifestations during the course of heliotherapy were carefully observed and recorded, and a comparative study made with the clinical course prior to treatment. Symptoms, physical signs, comparative roentgen plates and the general condition of the patient were all taken into consideration before arriving at a final conclusion. Twenty-nine cases were followed up for a year or longer after the treatment was discontinued. This afforded us an opportunity to learn whether improvement in any given case was ephemeral or of a more permanent nature, and whether an unfavorable course was favorably influenced after the treatment was discontinued. Reference to each symptom before and after the period of solarization will prove instructive.

Cough: Practically all cases, in which progress of insolation had reached a stage when the chest was exposed for 15 minutes, began to complain of increased cough and of a feeling of congestion or tightness in the chest. Auscultation elicited, over the site of the lesion, sonorous and quite fre-

quently large mucous râles. Five of the 9 fibroid inactive cases also complained of this peculiar feeling of tightness, but in them auscultation disclosed no noteworthy changes other than an occasional sibilant râle. Within a week or two after the exposure was increased to thirty or forty minutes, the cough gradually subsided and with it the annoying chest wheeziness.

This symptom is believed to be due to the local congestive action of the sun on the lungs. European observers consider this congestive phenomenon beneficial, because it tends to produce an active phagocytosis. Rollier is convinced that the sun-rays have a bactericidal and sclerogenic action on a deep focus in a bone, such as in hip disease, and he sees no reason why this should not be applicable also to a focus in the lung. There is no doubt that the sun-rays do exercise some immediate local action, but it is difficult to explain why this symptom should not become accentuated with an increase in dosage. As a matter of fact, the one or two-hour exposure case rarely complained. It is also inconceivable that a 15-minute exposure be sufficient to produce such a reaction, unless we assume this phenomenon to be allergic in nature. The clinical action of sun-rays is little understood, and any assumption would be purely speculative. Fluoroscopic and roentgen examination of 5 cases during this stage of apparent pulmonary congestion failed to disclose any discernible changes.

Expectoration: Cough as a symptom is no reliable index, for we know that cases with massive or progressive pulmonary involvement may not cough as much as those whose lesion is stationary or improving. The condition of the upper respiratory tract is an important factor in determining the extent of coughing, and so is also the intelligence of the individual patient and his ability to control the cough. Expectoration, on the other hand, is dependent chiefly upon the extent of pulmonary involvement and hence is fairly reliable in evaluating improvement.

In 13 of our cases the sputum decreased in amount on an average from 4 to 2 ounces, and in 3 of these the expectoration ceased entirely after ten months of treatment. With the exception of one, they all had advanced active lesions. A corresponding pulmonary improvement was noted in all except two. In one of these two the marked improvement of the laryngeal involvement was considered responsible for a decrease in both the cough and expectoration. In 26 the quantity of the sputum remained unchanged, although general improvement was noted in 10 and pulmonary improvement in 5. In 3 of the latter 5 the sputum decreased

after discontinuing heliotherapy. The remaining 11 cases had both cough and expectoration increased. They were all pursuing a very active and progressive clinical course, and discontinuance of the treatment had no effect on this symptom.

Tubercle bacilli: In eight cases the sputum yielded negative findings after an average of five consecutive monthly examinations. Marked general and pulmonary improvement was noted in all except one. Although one patient in this group had a complicating tuberculous epididymo-vesiculitis and cystitis, and developed an acute spondylitis after nine months of practically uninterrupted heliotherapy, the eventual outcome was very satisfactory. He is now ambulant, working as a barber 5 hours daily and is entering upon his thirty-first month of sun-cure. Thirty-six continued to have a positive sputum, although general and pulmonary improvement was noted in eleven. Five, with negative sputum at the beginning, remained negative, and one with negative sputum became positive. The latter was a striking instance of a case with an inactive upper lobe fibrosis, complicated by a tuberculous cystitis, whose pulmonary lesion became reactivated at the end of the eighth month. The high fever was at first attributed to a solar reaction, as physical signs in the chest were negative. The roentgen plate showed many areas of new infiltration. The course was rapid and fatal.

Hemoptysis: Of the 20 cases with a negative history of hemoptysis only 2 manifested this symptom while on heliotherapy, one by occasional blood-streaked sputum and one by a frank hemoptysis of two ounces. After the sputum became free from blood, the treatment, reduced in dosage to one-half, was resumed without any untoward effects. Of the 30 cases with a positive history of hemoptysis, 5 had repeated hemorrhages, necessitating discontinuance of the treatment, while 7 showed occasionally streaked sputum which would clear up in a day or two. In the latter, insolation was continued except during the period when the sputum was colored. Eighteen cases that had hemoptyses previously were remarkably free from this symptom during the entire period of sun exposure.

Temperature: There were only 4 cases whose fever gradually subsided to normal. One of this number was a young girl who for two years registered a daily afternoon temperature ranging between 99.5° and 100°F. The normal was reached after four months of heliotherapy. In all of these, general and pulmonary improvement was striking. In 10 the low-grade febrile course remained unchanged. Of these, 7 experienced

general improvement and 3 became worse. In 3 the subfebrile course became cyclic in character. At intervals of three to four weeks the temperature would suddenly mount to 102° or 103° F. and subside within three days. Discontinuance of exposure caused the disappearance of this symptom in one and no change in two. The latter finally succumbed to fatal complications. Of the 8 cases whose normal temperature continued within normal variations, 6 were improved and 2 had a progression of the pulmonary lesion. The 25 cases that were afebrile previously began to show a subfebrile tendency during the course of the treatment. This has no reference to the slight febrile rise immediately after an exposure. In this group the rise in temperature from normal to 99° or 99.5° F. persisted for several hours after an exposure. Four continued to pursue this febrile course for four to six months after discontinuance of the treatment, and in 5 hemoptysis became an annoying complication. In the remaining 16 no untoward effects on the general or local condition were noted, and the treatment was continued. When treatment was finally discontinued, the temperature returned to normal.

Pulse: An increase in the pulse-rate of from 10 to 30 beats was noted in all cases that had reached a period of insolation of one hour or longer. In some this phenomenon was noted after a much shorter period of exposure. A return to normal would usually occur within one-half hour. In 15 cases, however, the pulse remained accelerated 20 to 30 beats above its previous rate even during the intervals. In all of these the treatment was eventually discontinued; in 9 on account of progressive pulmonary involvement and in 6 because of persistent headache, dizziness and palpitation.

Weight: Ten patients gained an average of $10\frac{1}{2}$ pounds. Of these, 8 were generally improved and 2 showed a progression of the pulmonary lesion. Twenty-seven lost, on an average, 10 pounds each. Of these, 8 became progressive, 10 improved and 9 remained stationary. The 13 with no change in weight pursued a stationary course.

Pulmonary lesion: As already indicated, the effect of sun-treatment on the diseased areas in the lungs was determined by comparative physical and roentgen examinations. Of the total number, 18 improved. From further observation or follow-up of these cases for a little over a year we learned that one succumbed to an acute tuberculous laryngitis, one died from tuberculous meningitis and in one the fatality was due to a bronchopneumonia following hemoptysis. The latter case did not show a tendency to bleeding during the sun-cure period. Two are in

Eastern sanatoria, confined to bed with fever, and 2 are engaged in active occupations, feeling well. The remaining 11 are still in the sanatorium, pursuing a favorable course. Of the 22 whose pulmonary lesion remained apparently stationary, 5 are well and working, 4 suffered relapses and are confined to bed on account of fever, one is slowly convalescing from a profuse hemoptysis, in one acute intestinal symptoms became manifest, 2 have died, and 9 are improved, though not yet able to work. In 10 the pulmonary lesion became progressive. One improved after the treatment was discontinued, and succeeded in bringing to a quiescent state an acute laryngeal involvement. Four are progressively becoming worse and 5 are dead.

Blood findings: Only in 30 cases was there an increase in the lymphocyte count, averaging 10 per cent. In this group were 14 who definitely improved, 14 whose pulmonary lesion remained stationary and 2 who became progressive. Increase in hemoglobin and erythrocytes was not more marked than in other cases whose blood picture improved in high altitudes. The blood-pressure was lowered in all cases during insolation, but would return to normal within an hour.

Pigmentation: The degrees of pigmentation were carefully studied, with a view of determining whether this phenomenon has any prognostic significance, as claimed by some observers. The cases naturally subdivided themselves into four groups: (1) those who did not pigment at all; (2) those with slight tanning; (3) those in whom the skin assumed a moderately brown color; and (4) those whose skin became smooth, glistening and velvety, and resembling in color that of a negro.

Improvement or progression has reference only to the pulmonary condition. Of 11 cases in the first group, one improved, 5 became progressive and 5 remained stationary. The 4 in group 2 all remained stationary. In group 3, eight improved, 4 became progressive and 7 remained stationary, while group 4 lists 9 as improved, only one progressive and 6 stationary. This confirms the observation of others that good results from heliotherapy may be confidently expected in those who show a tendency to rapid and marked pigmentation.

Increased tone and development of musculature were noticed in only 6 cases. These gained in weight, and the general and pulmonary improvement was marked. The persistence of muscular flabbiness even in those who had marked pigmentation was disappointing.

Effect on complications: In 8 cases, though there was no apparent pulmonary improvement, the complications definitely improved. These

were: rectal fistula 2, tuberculous enterocolitis 2, spondylitis 2, costosternal abscess 1, and laryngeal and lingual tuberculosis 1. In 4 cases with pleural effusion the absorption of the exudate occurred much more rapidly than in those who were not exposed to the sun. In the few recorded bone lesions the results were most encouraging. In 3 cases of tuberculous epididymitis with open sinuses the discharge ceased, the induration decreased and the wounds finally closed.

Deaths: Five developed fatal complications during the course of heliotherapy. Two died from tuberculous meningitis, one from bronchopneumonia following hemorrhage, one from marked progression of the lesion following hemoptysis, and one from what appeared to be generalized miliary tuberculosis. The latter occurred in a case with an inactive fibroid lesion complicated by a tuberculous cystitis which followed a nephrectomy for renal tuberculosis. The spread of the pulmonary lesion was astonishingly rapid.

COMMENT

An analysis of our clinical report justifies the statement that we have, as yet, no scientific method of determining the physiological effects of sun-rays on the bodily mechanism. Schroeder (9) found that respiration is deepened, the alveolar carbon-dioxide tension reduced, ventilation improved, pulse-rate increased, blood-pressure reduced and skin capillaries dilated. We can confirm clinically at least three of Schroeder's observations, but to what extent do such physiological reactions exercise a beneficial effect upon the disease? Deep-breathing exercises are not indicated in advanced pulmonary tuberculosis; an accelerated pulse is usually an unfavorable symptom, and so is also a lowered blood-pressure. It is quite possible that such untoward symptoms as headache, dizziness, palpitation, faintness, etc., are due to the above circulatory changes. Improved elimination is always desirable in chronic, toxic diseases, but with our present knowledge of tuberculosis we cannot say that the elimination constitutes a problem of consequence.

On theoretical grounds a great deal should be expected from heliotherapy, since light is one of the three essentials to life, but it, not unlike another life's necessity, food, will inflict punishment on the human body if abused. From a study of the literature one is still left wondering as to the rôle played by the infrared rays or the ultraviolet rays. The more skeptical in the profession attribute the general tonic effects to the circulating air over the skin instead of to the sun's rays.

The rôle played by pigmentation is likewise not clear. There is no doubt as to its protective mechanism against burns, for those who are deeply pigmented can stand sun-exposure during summer afternoons for three and four hours without sustaining skin injuries. Bendes (10) cites the focusing of the *Thezac Persemeur* lens for 15 minutes on a pigmented skin with a resulting slight erythema which disappeared in one hour, while on an unpigmented skin with the same length of exposure a pronounced second-degree burn was the result. Protection, however, is apparently not the only effect, since clinical observations indicate that pigmented cases progress more favorably than those who fail to pigment. This again has its exceptions, for one of our deeply pigmented cases, who had been on heliotherapy for two years with marked general and pulmonary improvement, suddenly developed tuberculous meningitis that terminated fatally in three days. The autopsy revealed comparatively fresh tubercles, not only in the Sylvian fissure but also in the lungs, spleen, kidneys and intestines. Was that invasion due to an accidental breaking of a tubercle into an adjacent blood vessel, or was some obscure chemical action of the rays responsible for the spread?

Animal experimentation offers a fruitful field for investigation, but sufficient data are not as yet available. Rohde (11) rayed 5 infected guinea pigs and used two animals as controls. He came to the conclusion that experimental tuberculosis is favorably influenced by sunlight. Twichell (12) exposed 10 animals to sunlight and used 5 as controls. They were autopsied on the twenty-ninth day. While all showed widespread tuberculosis, there was a greater amount of involvement in the control animals. These experiments are suggestive but not conclusive, for it is difficult to tell to what extent the open air to which the experimental animals were exposed was a favorable factor and to what extent the comparative confinement of the control animals was an unfavorable factor. Besides, research workers have long since recognized the difference between the clinical manifestations of tuberculosis in the guinea pig and those noted in the human being. It is therefore extremely difficult to apply experimental observations to practical therapeutics.

Recently Colebrook (13) and his associates have shown that any skin irritant, whether it be ultraviolet and visible rays or heat and chemical agents, enhances the hemo-bactericidal powers. This was observed in experiments made to determine whether the serum or the leucocytes acquire increased power to kill such microörganisms as staphylococci, when man and animals are exposed to radiation, or when the cutaneous

surface is subjected to substances capable of producing irritation and inflammation. The authors believe that absorption into the blood of the products of tissue damage, or the enhanced absorption of normal tissue products produced by such damage, may be natural excitants of immunizing reactions, and shown biologically by the increased bactericidal power of the blood.

Such studies are of inestimable value, as they throw light upon some of our clinical observations. Definite constitutional reactions were noted in a great number of our cases. In 50 per cent this became manifest in a low-grade fever, which persisted until the radiation was discontinued. In 30 per cent there was an increase in the pulse-rate. These two phenomena alone suggest the possibility of absorption of some new toxic substances, which may or may not influence favorably the defensive body mechanism. A loss of weight in 54 per cent is unexplainable, unless by the assumption that such substances, when absorbed into the circulation, alter in some way the normal metabolism.

In this respect the effect of sun-rays is not unlike tuberculin. Schroeder is of the same opinion, and believes that the metabolic light effects run parallel with the specific antigens produced. The gradual or sudden change in the clinical course of a few patients after a period of exposure for one or two months, whether favorable or unfavorable, cannot be said to be a mere coincidence. The congestive phenomenon, spoken of above, suggests a focal reaction, and the fever and rapid pulse may be looked upon as a constitutional reaction. Whether specific antigens give rise to these reactions is an important question, and to what extent such reactions influence the course of the disease constitutes an urgent clinical problem.

On account of the uncertain or questionable effects of heliotherapy, Heusner (14) sent out 83 questionnaires to medical directors of sanatoria. Of 37 answers received, 9 were emphatic in disclaiming all value in heliotherapy, 12 questioned its value, 13 considered the general tonic effects valuable but noticed no influence upon the pulmonary disease, and only 3 claimed that radiation exercised a good influence on the process in the lungs. Liebe (15) reported 28 answers from observers who gave heliotherapy to only carefully selected cases. Specific beneficial results were denied by all, although subjective improvement was noted by a great many in the majority of their cases. A more extensive investigation of the results of heliotherapy as obtained in all sanatoria in this country, as well as abroad, would undoubtedly help to create a more definite and,

what is more important, a reliable opinion as to the value of this therapeutic measure.

SUMMARY

Fifty cases with an average period of one year under heliotherapy have been carefully studied. Forty had advanced, active disease, and of the total number 32 suffered from extrapulmonary complications. General and pulmonary improvement was noted in 18. One year after the discontinuance of the treatment 13 are more or less unchanged, 2 have had relapses and 3 are dead. Of the 32 whose pulmonary disease remained stationary, 14 experienced general improvement; and of these, 5 have acquired full working ability. Only 10 became progressive. One case with an inactive fibroid lesion developed an acute disseminating process. No definite effect was noted on the cough, expectoration or bacilli in the sputum. The slight changes noted cannot be attributed to radiation. The initial increase in cough and the feeling of tightness in the chest constitute an interesting but unexplained phenomenon. In 50 per cent, low-grade fever became manifest, and in some it persisted for 6 months after the treatment was discontinued. An acceleration of the pulse, of from 20 to 30 beats, was noted in 30 per cent. It is significant that 36 per cent with previous history of hemoptysis did not manifest this symptom during the course of treatment. While 20 per cent gained in weight, 54 per cent lost on an average of 10 pounds each. The loss in weight had no fixed relation to the general condition of the patient. Many improved or remained stationary despite the loss in weight. The only definite blood changes were an increase in lymphocytes, averaging 10 per cent in 60 per cent of the cases. The proportion of improved cases was much greater in the 30 per cent of those with marked pigmentation than in the others who showed little or no pigmentation. The extrapulmonary complications were invariably favorably influenced. In some, most encouraging results were obtained. The rapidity with which pleural exudates became absorbed is worth mentioning. Two cases developed bone lesions while under heliotherapy; one a tuberculous process of the 8th and 9th dorsal vertebrae, and the other a similar process of the second left metatarsal bone. Continuance of treatment yielded satisfactory results. Increased muscular development was noted in 12 per cent of the cases. These were the few whose pulmonary lesions were not very active, and there was little or no loss in weight at any time. It is worth recording that one

case, well pigmented, with marked improvement after two years of heliotherapy, died in three days from what appeared to be an acute tuberculous meningitis. The autopsy revealed miliary tuberculosis, involving the meninges, lungs, spleen, kidneys and intestines.

CONCLUSIONS

1. Heliotherapy in our experience has not yielded encouraging results in advanced pulmonary tuberculosis.
2. Neither the favorable nor the unfavorable results can be attributed with certainty to heliotherapy.
3. Heliotherapy is at least as dangerous an agent as tuberculin if used injudiciously.
4. There are many points of resemblance in the bodily reactions between radiation and tuberculin.
5. Hemoptysis is no contraindication to its use.
6. Extrapulmonary lesions are invariably favorably influenced by heliotherapy.

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OCCULT TUBERCULOSIS[1]

LOUIS M. WARFIELD

For the past two or more years I have been seeing now and then a case of which the following brief history is typical:

A woman, forty years of age, who had never married, complained of being run down. She had always been thin. She could keep up her work as an instructress in a school for the blind, but she was always tired. Off and on she had indefinite stomach distress with actual pain at times after or before eating. During periods of vacation she would feel pretty well, but soon after she returned to her work she again had this unaccountable feeling of weariness. Her menstrual periods were somewhat irregular, usually scanty, and now and then she would miss a period. She assured me she had never been ill in her life, but as she was about to leave she recalled that at the age of fourteen or fifteen she was so run down that she was taken out of school for a year and "built up." At the end of that time she weighed more than she had ever weighed before or since.

Physical examination revealed no striking changes in any organs or systems. Her build was of the extreme hyposthenic type. At the left apex I thought there was an old tuberculous lesion, and I thought I could make out increased hilum dulness on either side of the dorsal spine. Stereoscopic X-ray plates of her chest showed only a very slight haze at the left apex; the hilum shadows were not unusually large and the broncho-vascular tree was possibly a trifle more prominent than is sometimes seen. However, by no stretch of the imagination could the changes be interpreted as tuberculosis. Examination by specialists for foci of infection revealed none. Blood, blood pressure, urine, Wassermann reaction, and X-ray examination of the gastrointestinal tract were also devoid of abnormalities. She reacted to the intracutaneous injection of 0.1 mgm. O.T. in 0.1 cc. of saline solution with characteristic papule and hyperemic areola in 24 hours.

I am sure that such a history is not unfamiliar to most of you and that often you have been at your wits' end to know what to name the disease (if disease it is) and what to do for the patient. I know that many are labelled neurasthenia, many have had their appendices or their gall-

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bladders cut out, and many have had exploratory laparotomies for gastric ulcer. Far worse than any of these unfortunate accidents is an operation on the pelvic organs which many a poor woman has undergone.

How can we get at the source of the trouble and how can we remove the source when we find it?

My thesis is that these people are suffering from a type of tuberculosis called by Head (1) in 1916 *Concealed* and by Sewall (2) in 1920 *Occult*. And I propose to offer evidence which to my mind is incontrovertible. In order to grasp the situation thoroughly we must go back a bit and start at some fundamentals.

It is generally believed that everyone is infected with the tubercle bacillus at some time in his life, and the most universally accepted belief is that the infection takes place in infancy and childhood. The period between five and fifteen years is that of lymph-node, bone and joint tuberculosis; after that period the incidence of pulmonary tuberculosis rapidly increases, so that between twenty-five and forty years of age the largest percentage of deaths from lung tuberculosis occurs. These are well-known facts established by numerous observers in all parts of the world. The first infection produces a profound change in the reactivity of the body to further infection or to injection of the individual with tuberculin. In the normal uninfected guinea pig tuberculin is practically inert (Kolmer (3)). Following a certain period of inoculation with tubercle bacilli the guinea pig reacts violently, even fatally, to a comparatively small dose of tuberculin. What has happened? Here is a substance produced by the growth of the tubercle bacilli in bouillon which is quite innocuous to the healthy, uninfected animal but which is highly toxic for the animal infected with tubercle bacilli. Although there is some evidence that the inoculation of dead tubercle bacilli will produce the changes known as hypersensitiveness, we are not perfectly sure of the full meaning of this observation. We have absolute evidence that living bacilli do produce this change in body reactivity to tuberculin.

When tubercle bacilli first enter the body through any channel they are caught in the lymph nodes and there they set up a perfectly definite series of histological changes leading to the formation of tubercle. Usually the body reacts with a resulting protective capsule of fibrous tissue and the bacilli are walled off forever from the general circulation.

For a long time, years maybe, the person will show hypersensitiveness to tuberculin. It used to be thought that "once tuberculous, always tuberculous," but Krause (4), Gardner (5) and others have shown that clinically and experimentally known tuberculous lesions heal so completely that even hypersentitiveness is greatly diminished and perhaps lost, that is, the individuals no longer react to tuberculin and are probably in the original condition, in which an infection from without, instead of producing rapid hyperemic changes and quick healing, will again go through the slow process of tubercle formation.

Further, infection which results in demonstrable tuberculosis is usually from within. The possibility of there being such a mammoth dose of bacilli from without entering the body and producing the disease tuberculosis cannot be categorically denied, but the overwhelming weight of evidence points to infection from an already existing focus in the body as the origin of clinical tuberculosis. If we do not accept these dicta we must scrap our laboriously constructed schema of infection and reinfection in tuberculosis and begin at the bottom to build again. We must accept them at the present time.

On the one hand, then, we have tuberculous infection without symptoms or signs (what is present in the vast majority of us); on the other hand, we have the disease tuberculosis (let us make it specific by saying pulmonary tuberculosis) with definite symptoms and signs, fortunately not so universal a result of infection with tubercle bacilli. The final report of the Framingham Demonstration, a seven-year carefully planned survey, concludes that one in every 100 persons has active pulmonary tuberculosis and one in every 100 has the arrested or latent form. This conclusion is illuminating. What about these latent forms? Search the textbooks high and low and no emphasis is laid upon, scarcely mention is made of, this latent form. What happens when it begins to light up and, as Krause (6) says, the interchange of body fluids into the tuberculous area and of toxic products from the area into the blood take place? Here is where we have to cease talking fact and begin to speculate. But we are constructing an hypothesis on the basis of experimental and careful clinical observations, so we feel that there is some solid ground upon which to build.

There are multitudes of changes taking place in the body in its warfare against the tubercle bacillus. Sometimes the enemy advances but the attack is at once broken up and the *status quo* is again established. But if the positions of the defenders are undermined by some series

of accidents the attackers may gain a strategic position, and it is more difficult for the defenders again to bring about a truce. Now the enemy has grown stronger but still the defenders hold him in check. May there not, aye, does there not come a time when the enemy in a surprise attack temporarily overwhelms the defenders, but does not completely annihilate them? Are visible demonstrable objective changes produced? Not necessarily. But are other evidences produced which reveal the temporary advantage gained by the bacilli? I maintain that that actually happens and the evidence is that symptoms of various kinds begin to be felt by the defenders, that is, the patients. These symptoms are somewhat protean; they may be shown by any system or group of systems; the commonest expression is that the patient is "run down."

Suppose we catalogue the chief symptoms all of which have been noted in various patients at different times. The most frequent is *unusual fatiguability*. This may be either physical, the commonest type, or mental. The outstanding complaint of these patients is that they can no longer do the tasks which they formerly could do with ease and enjoyment. They start tired in the morning. The night's sleep does not seem to refresh them. They try longer hours in bed, but that does not give the usual restful feeling which they once had. This may last several weeks; then they begin to feel better, almost but not quite like their old selves, and they forget the tired feeling or attribute it to the weather, the season or to some other cause. Before long the feeling of lassitude again comes over them, this time possibly more profoundly. This periodicity of lassitude and well-being is most characteristic, and would seem to indicate clearly the growth and recession of the tuberculous process concealed somewhere in the body.

During this time there usually is slight but perceptible loss of weight. This may be regained during the periods of well-being. Vague symptoms grouped under the general term *neurasthenic* are also common, so that many of these patients, particularly the young women, are diagnosed as such, and are given tonics or are told to go away for a rest. Interestingly enough, a complete rest and change of environment often does put them back to a normal state, but again return to former life and occupation brings back the distressing train of symptoms.

The patients are easily chilled, suffer readily from cold, and shiver at the slightest draft. Often there is palpitation of the heart and throbbing in the head, with or without a dull headache, and usually

confined to the nape of the neck or the top of the head. There may be even a fine tremor of the outstretched fingers and a group of symptoms which has been termed *sympatheticoneuritic* (Kessel, Hyman, *et al.*). Fever may or may not be present. If one takes the temperature only occasionally at the office visit one rarely finds fever. The temperature is normal or even subnormal. Careful recording of the temperature for a few days at regular periods will most often show a slight but definite afternoon rise. However, just as important, it seems to me, is a continuous subnormal temperature. Fever may be present only after exercise as shown by me among a group of drafted men at Jefferson Barracks. It was thought that a differentiation could be made from neurocirculatory asthenia and mild types of so called hyperthyroidism by the temperature rise which followed exercise in this group of occult tuberculosis.

Finally, there is a group who complain of indefinite *gastrointestinal symptoms*. Pain of an irregular character, not having much relation to character of food or time of onset after food, is present. Many of these unfortunate patients present themselves with one or more abdominal scars, the results of operation for supposed gastric or duodenal ulcer or chronic appendicitis, or of some pelvic operation. The operation often temporarily seems to relieve them. It gives them a period of complete rest and assurance that the source of the trouble has been mechanically removed. Invariably, after an interval of weeks or months all the symptoms return in their original severity, and the patient's state is even worse, because his faith in doctors has been shaken. These people often seem to us to belong to the misfits in the world. They float from doctor to doctor in their attempts to find relief. They are dosed up with tonics until they become walking pharmacies and, finally disgusted with the members of the regular medical profession, they inevitably turn to the quacks and charlatans who promise them relief from their suffering.

DIFFERENTIAL DIAGNOSIS

The diagnosis of the cause of the complaints is not easy. It involves an intensive study of symptoms, signs and results of laboratory tests. In fact so exceedingly difficult is the diagnosis that it is usually not made. Only when some sudden open manifestation of tuberculosis jars both patient and doctor is it recalled that for a long time the patient has been "run down." Even then it is not always recognized that the

previous symptoms were the result of tuberculous infection, but tuberculosis is said to have occurred because the patient was run down.

A list of the most important diseases from which occult (concealed) tuberculosis must be differentiated is as follows: (1) syphilis, especially the hereditary form; (2) chronic focal infection, as of the sinuses, gallbladder, appendix, etc.; (3) early Hodgkin's disease; (4) mild types of Graves disease; (5) neurocirculatory asthenia; (6) certain blood diseases, such as idiopathic pernicious anemia, chlorosis, leukemia, Banti's disease; (7) gastric and duodenal ulcer; (8) diabetes mellitus. It seems unnecessary to go into detail in describing the points of differentiation among these various diseases and occult (concealed) tuberculosis. A mere cataloguing should call in mind at once the essential points. It will suffice to describe certain positive and negative points in substantiation of the diagnosis of occult (concealed) tuberculosis.

History: A careful history is most important. Inquiries into the adolescent period should be minutely made. Such illnesses as dry pleurisy, anemia over a long period, periods of amenorrhea in girls, any long illness leaving the patient in poor health for a time, periods of malaise alternating with periods of well-being, should be asked about. The family record should be searched for possible sources of tuberculous infection. Then, in the present illness, one should inquire about fever, unaccountable loss of weight, weakness, mental exhaustion, etc., etc.

Physical examination: One might as well admit at the outset that little can be elicited as a rule on physical examination of the chest. On inspection one often sees slight lagging of one side on inspiration. Often one supraclavicular fossa is noticeably deeper than the other. Over the posterior apex, opposite the 2nd to 4th thoracic vertebrae on one or the other side, there may be a visible swelling due to spasm of fibres of the trapezius and superior rhomboid muscles (Pottenger's sign). There is frequently transient flushing of areas of the chest and sweat is noticed to be running down the arms from the axillae. Palpation confirms the limitation of motion on inspiration and determines the spasm of the muscle fibres previously seen (Pottenger's sign). Occasionally vocal fremitus is increased. However, as there is a normal difference between the right and left apices, unless the left apex is the seat of some slight lesion, vocal fremitus will be different on the two sides, and I have not paid much attention to it.

On percussion one will often find very slight changes in pitch. These are not easy to detect. The changed note may occur over a very

limited area in the suprascapular space. Kronig's isthmus is narrowed. On auscultation one may hear either increased breath-sounds, with prolongation of expiration or suppression of breath-sounds. Either is significant. Occasionally one hears so called "granular" breathing. No râles are ever heard, but often fine scratchy friction sounds are audible. The signs are those which one will often find in apices known to have been infiltrated with frank tuberculosis and which are arrested or healed. There are cases when I have thought I could make out greatly enlarged hilum lymph nodes by the change in respiratory murmur, the enlarged nodes producing harsh breath-sounds. At times I have been right, again wrong, as shown by the stereoscopic X-ray plates.

Blood pressure: Sewall (7) has called attention to changes in the blood pressure from the lying to the standing position which he considers of great value in diagnosis. Vascular hypotension is the important feature, with lowering of the pulse pressure "usually far below 30 mm. Hg., with a progressive fall in systolic pressure or an inordinate rise of diastolic pressure upon assuming the standing position." I have been unable to agree altogether with these observations although I have found that his contention holds good in some cases.

X-ray: Here, where we might expect some help, we actually get little or none. Enlarged hilum lymph nodes, increased streaking of the broncho-vascular tree, even the so called "pussy-willow" appearance of bronchi or lymphatics or both, few or numerous calcified lymph nodes in the middle zone, slight haziness at an apex, slight streaking into an apex, one or all may be found in the chest pictures of absolutely healthy people. "Lymphatic tuberculosis" is often on the report from the X-ray laboratory, but it alone has no diagnostic significance. Van Zwaluwenburg and Grabfield (8) called attention to an apical pleuritis in some lungs. They called this a "pleural cap" or "line" and considered that "by insensible gradations these shadows pass into those of frank pulmonary tuberculosis." This pleural thickening is occasionally found in the chest plates of those suffering from occult (concealed) tuberculosis but it is far from being a common finding. So we may sum up the assistance we obtain from the X-ray examination by saying that in general it is negative assistance.

Tuberculin: After many years' experience with the use of Old Tuberculin I have come to regard it as a valuable aid in the diagnosis of these obscure cases. I am aware that opinion as to its usefulness has moved back and forth. In the help it gives in differentiating these cases from

cases with like symptomatology I consider it equal to the Wassermann reaction in obscure cases of syphilis. One-tenth of a milligram in 0.1 cc. of diluting fluid is injected intracutaneously into the skin of the forearm or anterior surface of the upper arm. A control of normal saline solution is injected into the other arm. This may seem to be a rather large dose, but I have used it for several years and have never seen any harm done in the class of case in which it is used.

We are testing hypersensitiveness. Not all adults are hypersensitive. It has been mentioned above that foci of infection may heal so thoroughly that hypersensitiveness is completely lost.

Kolmer (9) calls attention to the well-known fact that tuberculin injected into the tuberculous individual produces effects similar to those produced by exercise in the tuberculous. He considers that the *allergen* is produced in the tuberculous foci. This causes not only sensitization of tissue around the foci but also of distant organs, such as the skin. Such cells contain the allergic antibody. When tuberculin is injected it unites with these cells producing cellular allergic shock. This is shown by local hyperemia, and serous and cellular exudation at the place of injection of the tuberculin.

In a suspected case of occult tuberculosis a negative tuberculin reaction rules out tuberculosis as the cause of the symptoms. A very mild reaction lasting only twenty-four hours, and measuring only 5 to 10 mm., also means that tuberculosis is not the cause. But a reaction of 4 to 6 cm. in diameter, with local swelling and local heat and marked hyperemia, means extreme hypersensitiveness, and this, I believe, signifies that somewhere in the body, usually in the hilum lymph nodes of the lung, there is an active focus of tuberculosis, whence from time to time toxins escape into the general circulation. It has long been known that during the course of certain diseases hypersensitiveness to tuberculin is lost. It is not present in babies who are too young to have been infected with tubercle bacilli. It is also lost in cachexia from whatever cause, in advanced tuberculosis, and in rapidly fatal forms of tuberculosis, particularly tuberculous meningitis and acute miliary tuberculosis. The percentage of reactors increases throughout adolescence, until at forty years of age in some cities over 90 per cent react. But some do not react.

These, as has been said above, may be persons who have recovered from tuberculosis, or those who have been infected without symptoms and who have thoroughly healed their foci. The actual fact is that in

this country one finds a considerable number of adults who do not react to 0.1 mgm. of Old Tuberculin given intracutaneously; so that when a patient complains of symptoms of an indefinite nature, an intracutaneous test, when negative, shows positively that tuberculosis can be excluded as the cause of the symptoms.

A word should be said of the difficulty of differentiating the cases of occult (concealed) tuberculosis from a most important group of cases whose symptoms are the result of chronic infection of the accessory nasal sinuses. Dunham and Skavlem (10) have recently reported upon this group and have called attention to the interesting fact that a diseased sinus can be present with absolutely no complaint from the patient of symptoms referable to the head. Among 389 cases, which they had studied in order to determine the presence or absence of tuberculosis, 28 per cent of them were presenting symptoms like those of tuberculosis but were suffering from the results of other foci of infection. "And among these nontuberculous cases the primary focus outside the lungs has, in the vast majority of instances, been the head." Some of these cases did have indefinite lung signs which, however, were not due to tuberculosis but to the chronic infection of the sinuses. If this point is kept in mind differentiation of these obscure cases will be facilitated.

SUMMARY AND CONCLUSIONS

1. There is a large group of people who have indefinite complaints and who are not up to their standard of health.

2. These people, men and women, are usually suffering from some form of infection which is difficult to discover.

3. A certain number of these people are suffering from infection by the tubercle bacillus which does not express itself in frank textbook incipient stage but which expresses itself as a toxemia.

4. Such cases must be carefully studied and differentiated from early stages of other chronic infections.

5. The intracutaneous tuberculin reaction is of great value in the differentiation of this group.

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THE DEVELOPMENT OF CLINICAL TUBERCULOSIS FROM OCCULT TUBERCULOSIS[1]

LOUIS M. WARFIELD

If my contention that occult tuberculosis is the earliest symptomatic manifestation of infection by the tubercle bacillus be correct, I should be able to produce evidence of cases carefully studied over periods of several months, in whom no physical findings by any tests could be demonstrated and who then showed, either suddenly or gradually, unmistakable signs of clinical tuberculosis. I am prepared to produce this evidence by the citation of four case histories among pupil nurses in the Training School of the University Hospital. This is by no means all the evidence which I have accumulated. These cases, however, have been seen so often and have been followed so carefully by members of the Staff before I ever saw them, when they had reached the frank tuberculous stages of tuberculosis, that I do not hesitate to use them to prove my point.

Case 1: This young woman, age 19, entered the hospital September 8, 1921, complaining of pain around the heart. Both parents were living and in good health. There was no history of exposure to cases of tuberculosis. Her past history was that of the average young adult who had passed through the usual children's diseases with complete recovery from all. In 1919 she had a mild attack of influenza. She had had repeated attacks of tonsillitis up to the Autumn of 1920 when these were stopped by tonsillectomy. Menstruation began at 14 years and had always been a little irregular, but had never incapacitated her during the periods. She considered herself quite well and had lost no weight (weight 153 pounds).

The pain of which she complained was first noticed about July. It was around the heart and was stabbing in character. Nothing relieved the pain. This lasted about a week and then disappeared spontaneously. About five weeks before admission the pain reappeared in the same place and gradually grew worse. Nothing seemed to relieve it. It was more or less constant and was not made worse on taking a deep breath. She was strapped with adhesive

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plaster without relief and then entered the hospital for observation. She had no cough and no fever.

On examination she was a healthy, well-nourished young woman. Her color was good. The tongue was not coated. There was no fever. Except for the slight findings in the lungs the examination revealed no abnormalities. The thorax was symmetrical; expansion was equal. No dulness was made out anywhere. The spoken and whispered voice sounds were slightly increased over the right apex and between the right border of the vertebrae and right scapula. There were a few moist râles heard immediately beneath the right clavicle. Two days later the Ward Senior Interne noted that he heard some fine crackling râles over the left posterior apex.

Examination of urine and blood gave normal findings. The blood pressure was 125/80.

Stereoscopic X-ray films of the chest (P-A) on two occasions ten days apart showed the following:

> Chest is of medium length, rather broad, illumination is good. Position shows a slight rotation of the patient, the parietes are negative. In the right apex there is a definite thickening of the pleura with slightly more retraction; the retraction extends down well into the axilla. Costophrenic angles are somewhat overshadowed by the large breasts and there is some thickening of the broncho-vascular tree in this region, probably due to a chronic descending respiratory infection. On the left side there is a definite thickening of the pleura at the apex. The interspaces are wider on this side than on the right. There are a few smoky, hazy shadows in the apex underneath the pleural thickening, and extending down to the upper cornu of the left hilum. The costophrenic angle on this side is also somewhat overshadowed. The hilum on this side contains more than the usual number of opacities. The heart seems to be somewhat enlarged. It is normal in position. We are of the opinion that these shadows are of a distinctly suspicious nature. *Diagnosis:* Apical pleuritis.

The patient was kept on the ward for a week, during which time she had no complaints except the pain which gradually ceased, and temperature, pulse and respiration were normal. She was then discharged with the note that nothing abnormal could be found on physical examination. No diagnosis. After a week's rest she returned to duty. She carried on the strenuous duties of a nurse for a year, and was next examined December 12, 1922, when she again complained of pain in the chest. At this time examination by one of my most competent assistants, Dr. J. B. Youmans, revealed slight dulness at the left apex with increased voice and breath-sounds, but no râles were heard. He expressed the opinion that he did not believe she had active pulmonary trouble which caused her symptoms. He thought she was tired out and that the pains were psychic in nature.

About this same time (November 15, 1922) another stereoscopic X-ray set of chest films were taken and reviewed by Professor P. M. Hickey. His report was:

Stereoscopic plates of the chest show good curve of the right and left leaves of the diaphragm; there is no evidence of pleural effusion. The right and left lung fields are fairly well illuminated with lessened density in upper right and left. The hilum shadows on each side are somewhat exaggerated. The bronchial tree going to the upper right shows some slight beading which might class this case as a possible lymphoid tuberculosis.

Records of the Training School show that she was not off duty for a year before she graduated, October 5, 1923. About three months after leaving the School she felt badly, was examined and sent to a sanatorium for tuberculosis with a diagnosis of pulmonary tuberculosis.

Case 2: During routine physical examination of the nurses in October, 1921, Miss R. S., age 21, was found to have slight fever and tachycardia. She had no complaint. She was admitted to the hospital October 12, 1921, for observation and study.

Her family history was altogether without interest. In 1920 she had tonsillectomy. She had had the usual children's diseases, including a mild attack of scarlet fever at the age of nine. Otherwise her history was quite unimportant and uneventful. Her best weight was in February, 1921, when she weighed 116 pounds. Her weight on admission was 107 pounds.

Physical examination by the Ward Physician was quite normal except for a simple goitre and slight dulness at the left apex on percussion with a few crackling râles (?) which did not tend to disappear on cough. Both spoken and whispered voice sounds were normal in intensity. Routine P-A stereos of the chest were reported as follows:

They show a long, not deep chest, well illuminated equally throughout. The costophrenic angles are free. The apices show a thin pleural line beneath the lower margin of the second rib on both sides, more noticeable in the left than in the right. No abnormal shadows are seen in the immediate underlying parenchyma. The hilum shadows are not remarkable. There is no tendency toward grouping of opacities. The B-V tree is reticulated in type, practically uniform in distribution. The heart is normal in size and shape, of the pendulous type. *Diagnosis:* apical pleuritis.—Dr. Donaldson.

Examination of the blood and urine was normal. The blood pressure was 120/74. She remained in the hospital four days. There was no fever, the respirations were normal in rate, but the pulse ranged between 88 and 100 per minute. As nothing definite was found she was discharged to duty with instructions to return from time to time for examination.

For two years she was examined off and on. Nothing abnormal was ever found. She had periods of fatigue and of feeling badly but she kept at her work. At times she felt quite well. Her weight remained stationary. On September 22, 1923, she was examined because of the enlargement of her goitre. It was pulsating and she had tachycardia. The basal metabolic rate was found to be −8 per cent. At this time there was slight dulness over

the right apex with bronchovesicular breathing. (Reported by one of the Staff.) X-ray films of the chest were again made. One was lost. The report is based on one plate:

Symmetrical condition of the leaves of the diaphragm. No evidence of pleural effusion. Slight thickening of the apical pleura. We note some slight increase in density in the first and second left interspaces, also marked ramifications of the B-V tree going to the first and second interspaces in the upper right. These are the main interferences with the radiolucency of either lung field. We would conclude that the patient did present X-ray evidence of an early type of parenchymatous change.—P. M. Hickey, M.D.

On December 20, 1923, she was examined by Dr. J. B. Youmans, who reported that there was limited expansion on the left side, dulness at the left apex extending into first interspace in front, slight increase in breath-sounds and occasional crackling râles on cough. He considered that she had early tuberculosis at the left apex and advised sanatorium treatment. X-ray films taken again on December 22, and reviewed by Professor Hickey showed what he considered to be evidence of "definite parenchymatous lesion in the left apex. Compared with former plates we think this lesion is progressive." On January 3, 1924, she entered the Michigan State Sanatorium for Tuberculosis.

A letter from Dr. E. B. Pierce dated September 29, 1924, reads:

She began to fail in weight at once, although she ran no fever and the pulse averaged 85–95. She had hemorrhages in March, 1924. Tubercle bacilli were found in the sputum at that time. She ran a marked temperature of 102.6°F. Pulse rose to 100–120. Since March she had gradually gained in weight from 93½ to 103¾ pounds. Temperature has been normal since June. The pulse, however, remains high, and only very recently has averaged 80–100. She still coughs and raises, but there are no tubercle bacilli in the sputum at the present time. September examination shows the presence of râles over both upper lobes after cough. This is a marked extension from the first examination, which showed change in breath-sounds but no râles over the same areas.

Case 3: This young woman, a nurse in training, age 20, first came under our notice in May, 1923, when she complained of constant nausea. It was considered to be a mild gastric upset, and an antacid mixture was prescribed. She was no better in three weeks and again was seen, but nothing was found on physical examination. In June she complained of cough. Tracheitis was diagnosed. An X-ray set of stereoscopic chest films was taken:

Thoracic cage appears long and rather narrow. Leaves of the diaphragm are smooth. There is no evidence of pleural effusion. The trachea is in the midline. The cardiac shadow is not definitely enlarged. There is even radiability of the lung fields. The hilum shadows are slightly enlarged. There is some accentuation of the descending trunks on the right but no evidence of a parenchymatous lesion.

Up to November, 1923, she was better and worse, feeling at times fairly well, at times tired and out of sorts. She began to have pain in the stomach and

"dyspeptic" symptoms. Still nothing was found on physical examination. In order to determine whether her symptoms were due to hyperthyroidism a basal metabolic rate was taken. It was reported + 2.7 per cent, with average pulse of 96. Still later she was again seen, complaining of pain in the chest and back.

On March 29, 1924, she was admitted to the hospital with the complaint of pain in the right thorax and midaxillary line. Five weeks before this time she was seen in our Out-Patient Department because of pains in the chest. A diagnosis of chronic bronchitis was made by a competent member of the staff. Under treatment her pain was relieved in two to three days. Four weeks ago her tonsils were removed. She made an uneventful recovery. Two weeks ago she again had sharp pains in the right side; they were constant, and aggravated by exertion, and were worse at night. For a week she had had a dry cough. Two weeks ago, when the pain started, she had chills and sweating at night. For two months past she noticed tachycardia and dyspnea on slight exertion. The family history was negative and there was no history of exposure to tuberculosis. She was a healthy girl and except for chronic constipation was well up to May, 1923, when she began to have the series of complaints outlined above.

On examination she had all the signs of effusion into the right thoracic cavity, the dulness in the back extending up to the middle of the scapula. There were fever, rapid pulse and slight increase in respiratory rate. The urine was negative. The blood showed Hb. 65 per cent (Talquist); R. B. C. 4,600,000; W.B.C. 8,600; differential count normal. Blood pressure was 108/70. Thoracentesis withdrew 1100 cc. of yellow, slightly cloudy fluid, sp. gr. 1.022, predominating cell was a lymphocyte with few red blood cells. No tubercle bacilli were found in smears, and guinea pigs inoculated with fluid did not develop tuberculosis. She had irregular fever for several weeks, and developed a pneumothorax which was diagnosed on physical examination and confirmed by X-ray plates of the chest. After six weeks she was discharged. Her temperature had been normal for two weeks, her weight had increased, her appetite had returned. There was still slight dulness at the right base but no fluid was present. She was going to a sanatorium. Several X-ray plates made from time to time confirmed our physical findings that there was no parenchymatous lesion at either apex.

Case 4: This nurse was in the hospital as a patient in 1920, when she was 18 years old. At the time it was suspected that she might have infection with the tubercle bacillus but it could not be proved. (No tuberculin test was given.) She was sent back to duty and worked until July 6, 1924. Except for unaccountable underweight she said she had felt fairly well for the past three and a half years. She was admitted to the hospital on July 7, 1924,

complaining of headache and backache. The onset of her illness was sudden, with dull, dragging, intermittent pain in the lower back, and severe frontal headache. Her temperature was 102.2°F. Since the first of May she has had an occasional "stitch" in the left lower chest, especially when the weather was damp or she drew a long breath. There was no cough or night sweats. Two years ago she weighed 121 pounds. On admission she weighed 110 pounds.

She was an only child. Her father died as the result of an accident when he was 43 years old. Her mother died at 39 years. She did not know the cause of death.

Except for the indefinite illness in 1920 and a tonsillectomy in 1922, she has been usually healthy.

On physical examination there were dulness and absence of breath-sounds for about 10 cm. in the lower left back. Signs of compression were present at the left apex. The right lung was clear. X-ray plates confirmed trouble at the left base, which was thought to be due to thickened pleura. There were no evidences of parenchymatous changes in the apices. She had an irregular, rather high fever and a rapid pulse. The urine was negative. Leucocytes were 12,500. O. T., 0.1 mgm. intracutaneously, showed a marked positive reaction in 24 hours on July 8th. In a few days positive signs of fluid were found in the left thoracic cavity. This was confirmed by X-ray plates. Thoracentesis withdrew 400 cc. of greenish-yellow exudate, all the cells of which were lymphocytes. Tubercle bacilli were not found in smears of the fluid, culture showed no growth of bacteria, and guinea-pig inoculations showed no tuberculosis. After thoracentesis she rapidly improved and left the hospital September 12, 1924, to go home and continue treatment.

DISCUSSION

Only a brief discussion seems necessary to clear up certain questions which will occur to any reader.

First, if I believe so firmly in the value of the intracutaneous tuberculin test, why did these patients fail to receive it? The answer is that my connection with the University Hospital dated from July 1, 1922. These cases were seen and studied prior to that date, or were seen by my assistants in the Out-Patient Department who were not convinced that tuberculin was of great value, and who did not call my attention to the fact that these cases were coming again and again to the Out-Patient Clinic. Only within the past few months have certain members of the Staff been convinced of the value of tuberculin in just this class of cases.

Second, why were not all these young women suspected of being victims of the toxemia produced by infection with the tubercle bacillus and then treated accordingly? I cannot give the answer to this. I only know that this explanation for many indefinite symptoms leading to ill health is not taught to medical students in as emphatic a manner as it should be taught, and when they become doctors of medicine they know little or nothing about the tubercle bacillus as a cause of any disease but outspoken clinical tuberculosis.

In case 1 the lung findings were so indefinite, and the X-ray plate revealed only what is so often seen in people who have recovered from slight pleuritic apical lesions, that it seemed justifiable to make a diagnosis of "no disease found." Here again it was reported that the pleural line described from this clinic by Van Zwaluwenburg and Grabfield (1) was present. This is looked for here and reported, it seems to me, rather frequently in normal people. A year passed before the patient had symptoms again. Then she had slight changes at the left apex which were those of a healed lesion and "lymphoid tuberculosis" reported from the X-ray laboratory. Another year passed, she finished her training, then felt bad, and pulmonary tuberculosis was diagnosed.

Case 2 was seen two years before she developed evident signs of pulmonary lesion. After her stay in the hospital in 1921 she apparently seemed in fair health until 1923. But during those fateful two years she was not always as well as she should have been. Now she has had hemorrhages, tubercle bacilli in the sputum, and is slowly convalescing in a sanatorium.

Cases 3 and 4 show that primary serofibrinous pleurisy may be the outspoken lesion after a long period of ups and downs. One might say that there is a question of the etiology in these cases, as no tubercle bacilli were found in smears of the fluids and the guinea pigs inoculated with the fluids did not develop tuberculosis. While it would have been a satisfaction to show tubercle bacilli, I feel sure that enough evidence has accumulated during the past twenty years to leave no doubt that practically all primary pleurisies are tuberculous in origin. In the absence of any other evident cause I think we may accept the tubercle bacillus as the cause of the pleurisy in these two cases.

CONCLUSIONS

The conclusions drawn from a study of cases, of which the four reported here are types, are two:

First, there is a very definite train of symptoms caused by the tubercle bacillus growing in the body, the symptoms are protean in character, the patients are not absolutely ill, but they are more or less incapacitated for their best work. This is occult tuberculosis.

Second, these cases are proved to be due to infection with the tubercle bacillus by the course and progression of the symptoms and signs which at times lead gradually and by insensible stages to actual demonstrable tuberculosis.

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OCCULT TUBERCULOSIS WITH GASTROINTESTINAL SYMPTOMS[1]

LOUIS M. WARFIELD

Recently (1) I have reviewed data which show that infection with tubercle bacilli gives rise to a series of vague and indefinite symptoms due to absorption of toxic products from concealed tuberculous foci. The symptomatology of these cases is protean in character, and the diagnosis is not always easy. I have also presented case reports (2) which show that months after the beginning of symptoms of toxemia there is some manifestation of clinical tuberculosis, so that there is a logical progression of the growing tubercles in the body from the time of indefinite toxic symptoms to actual demonstrable tuberculosis. This appears to me to be of great importance in the campaign against the spread of tuberculosis as far as any one individual is concerned. The treatment of these cases is usually simple and successful, provided always that there is complete coöperation on the part of the patient.

In this paper I propose to report cases of occult tuberculosis in which gastrointestinal symptoms were so prominent that diagnoses of gastric and duodenal ulcer and appendicitis were made. One man (case 4) had his appendix removed some years before I saw him. When he presented himself for examination there were demonstrable signs of pulmonary tuberculosis.

Many of the patients are diagnosed as having gastric neurosis. A few years ago that diagnosis was commonly made. At present I do not believe we are ever justified in making such a diagnosis. Neurosis there may be, but it is secondary to some definite lesion, which may elude our diagnostic skill but which nevertheless is there. The term *neurasthenia,* so overworked some years ago, should also be so limited in its use that probably it too had better be dropped. It is a confession of our ignorance of the cause of the symptoms from which the patient is complaining. There is entirely too great a tendency to the loose use of omnibus terms and too little accurate, intensive study of obscure cases. We should all cultivate careful thinking and direct speaking so that when we do talk we really mean what we say.

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Case 1: A single woman, 44 years of age, social-worker with the deaf, complained of stomach trouble which she had had off and on for several years. Pain after eating was her most important symptom, although the pain was apt to come on when the stomach was empty. It had no particular relation to food. She had become afraid to eat, as the pain at times was so severe that it doubled her up. It was always in the pit of the stomach, but had no great tendency to be felt in the back. She had had no nausea or vomiting. She had been treated for "ulcers of the stomach" from time to time, but had never had more than temporary relief. Besides her own work she had the care of a mother invalided with arthritis.

There was no tuberculosis in the family history and no history of her exposure to the disease. Up to fifteen years of age she was a strong, well girl. Menstruation began at 14 and was not unusual. About the age of 15 she was "run down," had some stomach complaints, ceased menstruating for 7 months, had headaches, and lost weight. She was said to be threatened with tuberculosis, and was kept from school for a year. Following this period she seemed to recover, but menstruation became painful and at every period she had nasal hemorrhages. She was told she had an infantile uterus, and at about the age of 23 she had electrical treatments *per vaginam*. Several years ago she had a severe attack of typhoid fever. Since then her bowels have been irregular, with a tendency to looseness. Four years ago she was much pulled down by a series of furuncles on her arm. She has no fever and no cough. Her appetite is fitful. She has headaches at the back of the head, going up to the crown. She is about 15 pounds under weight. A few days before she consulted us she had strained the sacroiliac ligaments while lifting her invalid mother. This made all her symptoms worse, so that she was incapacitated for work.

On physical examination she was a tall, thin, narrow-chested woman with long fingers and flat pelvis. The bony framework was prominent, the costal angle was acute, a typical hyposthenic type. There was nothing abnormal found in the head, throat or neck. The heart was "dropped" in type, but the sounds were normal. Chest expansion was limited in general, with lagging on the left side. There was slight impairment of percussion note at the left apex and increased hilum dulness. The breath-sounds were harsh, expiration was prolonged, whispered voice sounds were much increased. No râles were heard anywhere over the lungs. There were no definite changes at the right apex.

The abdomen was flat. There was questionable stiffness of the upper right rectus muscle on careful palpation. Both kidneys were felt. All the reflexes were present but were hyperactive. The urine was normal. The Wassermann reaction was negative. O.T. reaction was strongly positive in twenty-four hours. There were no abnormalities found upon careful X-ray examination of the gastrointestinal tract. Stereoscopic X-ray films of the lungs showed slight haze at the left apex, possibly increased hilum shadows with a few

scattered calcified spots in the hilum and in the middle lung zone, possibly slight increase in visibility of the broncho-vascular tree in the first and second interspaces on both sides, and an elongated, narrow heart.

Case 2: A young man, age 34, a metre-reader, complained of pain in the back and stomach trouble: "food lays and ferments and don't give me any strength." For the past 3 years he has had belching and a feeling of fulness in the abdomen. There was some pain which had no relation to meals. The gas in his stomach pressed upon his heart and made him short of breath. He was weak and unable to do a full day's work. For some time he had had slight fever, 99° to 100°F., almost every day. Since the onset of his illness he had lost weight gradually, from 148 to 122 pounds. He had not worked at all for the past two months and had been in bed for the past month. His father died at age of 55 of stomach trouble (tuberculosis?). The family history was otherwise negative. He had always had good health up to 3 years ago. His habits were good. He denied venereal infection.

On physical examination he was a fairly well-developed and nourished man of normal build. The only finding in the lungs was rough breath-sounds at the left apex. Nothing abnormal was found in the heart or the abdomen. The reflexes were present and very active. There was partial hemianesthesia to pin-point, and there was anesthesia on the right conjunctiva. Provisional diagnosis by the ward interne was hyperacidity, gastric ulcer (?) and anxiety neurosis.

The examination of urine and blood revealed no abnormalities. The Wassermann reaction was negative. An Ewald test meal gave free HCl 8. O.T. on the arm gave very marked reaction in twenty-four hours. Gastrointestinal X-ray examination was not abnormal. Stereoscopic X-ray films of the lungs revealed only the so called "pleural line" described from this Clinic by Van Zwaluwenberg and Grabfield.

Case 3: A railroad foreman, age 52, complained of pain in the stomach dating back about 6 months. The pain was chiefly on the left side, had a tendency to run through to the back, and was much worse during the day when he was working. It was uninfluenced by food. There was no nausea or vomiting. The patient had perceptibly lost strength, had lost about ten pounds in weight. He had been treated by doctors, but was growing worse instead of better. In the family history there was nothing of importance. His past history revealed only the usual children's diseases and mild influenza three years ago. His habits were good and he denied venereal disease.

On physical examination he was a well-built, well-nourished man. There was nothing of importance found in the head or throat. The lungs were reported to be negative. Careful reëxamination revealed only very slight

changes at the left apex like those noted above. The heart seemed normal. The abdomen was natural in appearance. There was decided pain on pressure in the epigastrium. The provisional diagnosis by the interne was gastric ulcer.

The urine and blood examinations were normal. The Wassermann reaction was negative. No free HCl was found in the stomach contents following an Ewald test meal. There was a marked reaction to O.T. in twenty-four hours. Gastrointestinal X-ray examination showed normal tract. Stereoscopic X-ray films showed only a slight increase in visibility of the broncho-vascular tree in the upper left lung.

Case 4: This patient, a Jewish merchant, age 32, was observed in the Out-Patient Department. His chief complaints were heartburn and bloating after eating. He definitely dated his trouble to 8 years ago, when be began to have these symptoms. He was treated for a year for stomach trouble, and then appendicitis was diagnosed. His appendix was removed. For a short time he felt better; then his symptoms returned in worse form. He has attacks of heartburn and distention 5 to 10 minutes after meals, but not after every meal. There are some days when he has no attacks. Any kind of food has brought on the attacks. His diet has been reduced to vegetables. He drinks a great deal of water, and has been taking sodium bicarbonate for months. He found that a daily enema made him feel better. His tonsils were thought to be the cause of his ill health; so they were removed 8 months ago. He has lost no weight, and did not know whether or not he had fever. There were no night sweats or cough. The family history was unimportant and the past history revealed a healthy young man up until the onset of his illness 8 years ago.

On physical examination he was a muscular, well-nourished man. The only important finding was in the lungs. At the right apex the percussion note seemed dull and the breath-sounds and whispered voice sounds were increased above the normal. At the left apex, from the first interspace anteriorly to the spine of the scapula, there was dulness on percussion. On auscultation the breath sounds were bronchovesicular and sticky, and crackling râles were audible during inspiration and after cough. A diagnosis of active pulmonary tuberculosis was made.

The Wassermann reaction was negative. Roentgenological examination of the gastrointestinal tract revealed no abnormalities. Stereoscopic X-ray films of the lungs revealed bilateral apical tuberculosis with fibrous tissue formation.

DISCUSSION

Complaint of stomach trouble is one of the commonest of all complaints in early as well as in advanced lung tuberculosis. In 1894 W.

Soltau Fenwick considered that dyspeptic symptoms occurred more often in females than in males. As a rule he thought that these symptoms occurred more often in that variety of phthisis which commences insidiously and progresses slowly. In all the textbook articles on pulmonary tuberculosis mention is made of the gastrointestinal symptoms, but little or no stress is laid upon these indefinite stomach complaints as the very earliest evidence of tuberculotoxemia. After long and varied experience I am convinced that there is no set of symptoms so grossly misinterpreted as the dyspeptic symptoms of the so called pretuberculous stage.

Groover and Christie (3) reported upon a series of 1300 cases sent to them for X-ray gastrointestinal study. The conclusions drawn from their figures are an indictment of many who are licensed to practice medicine. They show the deplorable trend of much of the modern medical education, in which students who are learning medicine are not trained to use the means with which nature has endowed them,—hands, eyes, ears, brain,—but observe their instructors throwing all the burden of making diagnoses upon the various laboratory procedures, such as the difficult Wassermann reaction, the special technical procedures in blood chemistry, the elaborate X-ray examinations, etc. The consequence is that patients are no longer always carefully examined by the doctor, or even by the instructors and professors in our best schools, nor is an honest attempt made to arrive at a diagnosis after careful study of the case. A cursory history instead is taken, a superficial physical examination is made, and then the patient starts on his round of the various specialties and laboratories. Apparently it is expected by the physician in charge of the case that surely in one laboratory or by one specialist the diagnosis will be made. The authors found, in the 1300 referred cases, actual pathological lesions in 506, or about 39 per cent. Unsuspected lesions were found in the chest in 170 cases. Of the cases referred for gastrointestinal study, about twice as often pathological lesions were found in the gastrointestinal tract as in the chest. There were 98 cases of the group in which the symptoms were on the part of the gastrointestinal tract but the lesions were exclusively in the lungs. Of these, 84 were definitely due to tuberculosis and 14 were cases of pleural effusion, unresolved pneumonia, spontaneous pneumothorax, malignant disease, pleural adhesions and bronchiectasis.

The four cases briefly outlined above are chosen at random from among a large group seen and studied during the past few years, and represent

more or less typical histories of such patients. The ages are seen to be from 32 to 52. Both men and women are affected The oldest patient I have studied was a physician aged 55, the youngest a girl aged 20. In other words, the people in this group are just in the age period when pulmonary tuberculosis is most common. Case 1 represents a class in which, in early adolescence, there was evidently a real infection with the tubercle bacillus sufficiently severe to produce profound ill health. In this period of life lymph-node and bone tuberculosis are most common. Symptoms in girls of great importance at this age period are anemia, chlorosis (?), amenorrhea, and gastrointestinal complaints. In boys, except for the amenorrhea, the complaints are the same. Case 2 represents a type of case in which there is apparent health until adult life, but in which there is evidence that one or the other parent was the source of infection. Pearl (4) says in a recent book in a chapter on *Constitution and Tuberculosis:*

> In so brief a space it is wholly impossible to marshal more than the smallest fraction of the pertinent evidence which bears upon this problem. All that has been attempted here, and if that has been accomplished I am satisfied, is to demonstrate in the first place, that the problem of the causation of breakdown with clinically active tuberculosis, is a problem of tremendous complexity and difficulty, toward the solution of which only the merest beginning has been made, and in the second place, that the inherited constitution of the individual is a factor in the problem of a great deal more than the negligible importance which some in high positions would accord it.

In case 3 still another group is represented, the individual past middle life with no history of serious previous illnesses or of evident sources of infection at home or at his work, yet who shows unmistakable evidence of toxemia, in my opinion, by tuberculosis of concealed or occult type. In case 4 we have the story of the mistaken diagnosis, the useless operation, the periodicity of symptoms to which I called attention in a recent article on *Occult Tuberculosis,* and the gradual development of clinical pulmonary tuberculosis after 8 years of warning that it might come to pass.

It is strange that so little is said in the textbooks about this toxemia of tuberculosis. The only articles dealing specificially with this important phase of tuberculosis are those by Head (5) and by Sewall (6). It is easily understood why the experts on tuberculosis have not called attention to this type. They never see these cases. People go to their family physician who has not been taught the significance of the indefinite symptoms which may characterize this "pretuberculous" yet still

tuberculous stage. There has been mention from time to time of a pretuberculous stage. My contention is that this is the result of tuberculosis. It is only pretuberculous in the sense that it antedates the demonstrable clinical tuberculosis. Patients then go to the gastric specialist who almost invariably diagnoses "gastric neurosis" (but may diagnose gastric ulcer), gives some tonic and lays out a diet. This regimen does often help temporarily, and patients go away for a vacation and come back ready and anxious to resume their daily activities because they feel so well. Some never have any further complaints and remain well. Others begin before very long to have the same train of symptoms which they previously had. Again they seek advice of the gastroenterologist. Again drugs and diet are given. This time there is no relief. Pain may now be a prominent symptom; so operation is advised and performed. A normal appendix is removed or it is found, much to the surgeon's chagrin, that there is no gastric or duodenal ulcer. Finally, the patient begins to cough, has fever, and goes to a lung specialist who has no difficulty in diagnosing incipient (?) pulmonary tuberculosis. A pertinent question arises here. When is pumonary tuberculosis incipient? Is it during the period of symptoms without signs, such as in the cases I have described, or is it at the period when by physical examination signs characteristic of pulmonary tuberculosis can be detected? I say that this is an important question for the phthisiologists to settle. The specialists who reside and work only in sanatoria for tuberculosis do not see this type of case except when some insistent individual sends a case to them, as I have done. I am then informed that no tuberculosis can be found by physical examination or by X-ray films of the lungs. I am aware of that fact. I could not find signs myself, but I feel positive that the patient should be treated now so that tuberculosis will never be found.

TREATMENT

Treatment, in my experience, if carried out properly and consistently is just as successful as malaria treated with quinine, or early syphilis treated with mercury and arsphenamin. For several years past I have had the very definite feeling that pure unadulterated codliver oil was a specific in these cases of occult tuberculosis. Recently I have found most interesting confirmatory evidence of this empirical treatment.

Campbell and Kieffer (7) conclude, from a very careful experimental

study of the action of codliver oil on the tubercle bacillus, that the drug exerts a definite inhibitory and bactericidal action on virulent tubercle bacilli. Cottonseed oil controls showed little or no inhibition, and this oil was not at all bactericidal. They say that the codliver oil, extracted with as little heat as possible and not refined, had in their experiments a more potent action than the oil otherwise extracted.

Kirschner (8), in a report on codliver oil in the treatment of tuberculosis, comes to the following conclusions:

1. The oil is a very valuable remedy in the treatment of tuberculosis.

2. Its value is dependent upon a number of different factors: (a) it is a concentrated fat food; (b) it promotes absorption of other fats; (c) it limits respiratory ventilation; (d) it has a destructive action on the tubercle bacillus; (e) it has a large fat-soluble vitamine A content; (f) it favors absorption and deposition of calcium in the tissues.

Finally, Professor H. C. Sherman of Columbia University, at the meeting of the British Association for the Advancement of Science held at Toronto, Canada, in December, 1923, showed that rats fed on diets deficient in vitamine A (fat-soluble) "showed a striking tendency to break down with lung disease at an age corresponding to that at which pulmonary tuberculosis so often develops in young men and women. The bacillus is different," but the lesions were very smilar in the lungs of the rat to those in the lungs of human beings caused by the tubercle bacillus. He also called attention to the now well-known facts that butter is rich in vitamine A but that codliver oil is the richest in vitamine A of any known substance. Carrots are richer than potatoes or turnips, spinach is richer than lettuce, and green celery is richer than the bleached leaves.

Now we have scientific evidence of the value of codliver oil in the treatment of these cases of occult tuberculosis. *The oil should be raw.* It should be taken in sufficient doses, drams 2 to 4 (8 to 16 cc.), three times daily after meals, and it should be continued over a long period of time,—at least 3 months. It may then be discontinued for a month and again taken in smaller doses. Treatment should continue for at least a year with intermissions now and then. Naturally, no drug will act unless it is given a chance; so that the hygiene and diet of the patient should be attended to, and the patient must coöperate to the best of his ability.

CONCLUSIONS

1. A few histories are given, showing types of gastrointestinal symptoms in occult tuberculosis.

2. These cases are not usually seen by the specialists in tuberculosis, especially by those who work in sanatoria, but by the general practitioner or by the specialist in gastroenterology.

3. These cases are the really incipient case of pulmonary tuberculosis.

4. In the treatment codliver oil is a specific drug.

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COMPLEMENT FIXATION IN TUBERCULOSIS WITH WASSERMANN'S ANTIGEN[1]

MAX PINNER

In March, 1923, Wassermann (1) described a new antigen for complement fixation in tuberculosis. His statement that "every human being, child or adult, whose serum reacts positively with the tetraline-tuberculosis-lecithin-antigen, does not only harbor tubercle bacilli, but has also tuberculous tissue from which he absorbs and against which he reacts, that means that he suffers from an active tuberculosis," has naturally drawn much attention to this new antigen.

The antigen is prepared by extracting tubercle bacilli at incubator temperature with tetraline (a tetrahydrated naphthaline) in a shaking machine. This process leaves, after several weeks, a material which has lost its acid-fastness. The dried residue has powerful antigenic properties, and a sheep, which was repeatedly injected with this powder, developed complement-fixing antibodies, not only against this powder, but also against tubercle-bacilli emulsion and O.T. However, sera of tuberculosis patients did not deviate complement with this antigen. The addition of the substances extracted by the tetraline (lipoids, wax, and fat) did not change this fact. If, however, a small amount of lecithin is added to the extracted bacilli, the antigen gains the qualities stated above. Wassermann explains this mechanism by assuming that the serum of an immunized but not diseased animal contains only antibodies against tubercle bacilli, but that the serum of a tuberculosis patient contains, in addition to this, a lipoidophile factor, derived from cell-destruction. He believes that only a definite mixture of tubercle-bacilli protoplasm and lipoids makes a specific indicator for active tuberculosis. Such a mixture is, for example, Besredka's antigen, on account of the egg lipoids which it contains, but in this case the quantitative relation is not at its optimum.

Klopstock (2) showed that the lecithin itself does not enter into the antibody-antigen complex; but the addition of some lipoid causes the

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formation of "those invisible flocculations which bring about the complement-fixation reaction." He proves that the lecithin acts as a "sensibilizator" in other kinds of protein precipitations, such as in the Esbach test. Klopstock concludes that in tuberculous sera with a very large amount of antibodies "the number of the antigen-antibody complexes is so large that the homogenicity of the serum becomes disturbed even without a lipoid," but that in most of the tuberculosis sera with a smaller amount of antibodies the addition of a lipoid is necessary in order to make the antigen-antibody reaction manifest.

Wassermann tested his antigen with sera from patients suffering from syphilis and carcinoma, and from pregnant women, and never found nonspecific fixations. He does not mention in how large a percentage of cases of active tuberculosis he obtained positive results, but remarks that some of the active patients gave negative reactions. This occurrence is supposed to indicate "frequently the tendency to a severe and progressive course; it indicates a rapidly disintegrating torpid tissue which is not sufficiently capable of a biological reaction." Wassermann states that this test will be of importance in doubtful cases, especially in suspected tuberculosis of children. Numbers of investigators have since reported on their experience with this new antigen.

LITERATURE

The value of a diagnostic serum-reaction for active tuberculosis must be determined by the percentage of positive results in active and nonactive patients, and by the percentage of nonspecific reactions. Table 1 gives a brief survey of the results obtained by various investigators.

Most of the authors found the antigen not to be absolutely specific; even Kalcher and Sonnenfeld, who do not report any nonspecific fixations, obtained 19 per cent positive reactions in inactive tuberculosis. Lange and Heuer, and Janssen, have too small a number of nontuberculous cases to give a definite judgment. All of the investigators report that the negative reactions in active tuberculosis are by no means obtained only in prognostically unfavorable cases. The nonspecific reactions were found chiefly in cases of syphilis and pregnancy. Klopstock (13) used Wassermann's antigen in experimental studies on guinea pigs and found that normal guinea pigs never gave a positive reaction. In artificially infected animals the reaction became positive usually in 11 to 14 days after the infection; the reaction changed in an irregular

manner from positive to negative, and in one infected animal remained negative throughout the disease. Klopstock remarks that any antigen demonstrates only those antibodies which are formed *in excess* to the resorbed antigens in the body.

METHOD AND RESULTS

In our tests the directions given by Wassermann were strictly followed, with the sole exception that in most of our tests not three different amounts of serum were used but only one; this was done in

TABLE 1

NAMES OF AUTHORS	NUMBER OF CASES	NUMBER OF ACTIVE TUBERCULOSIS PATIENTS	PERCENTAGE OF NEGATIVE RESULTS IN ACTIVE CASES	NUMBER OF NON-TUBERCULOSIS CASES	PERCENTAGE OF NONSPECIFIC REACTIONS
Janssen* (3)	72	50	12	2	0
Jacob and Moeckel (4)	248	200	17	48	16.4
Gaethgens and Goeckel (5)	416	198	60	211	8
Mylius (6)	164	60	63	41	14.6
Kalcher and Sonnenfeld (7)	202	165	53.9		0†
Schlossberger, Hartoch, Lusena and Prigge (8)	?	?	29.4	?	29.2
Winkler and Gerth (9)	191	?	25	?	9
Lange and Heuer (10)	220	?	ca. 50	8	0
Silberstein (11)	334	147	ca. 57	130	ca. 30
Richter (cattle as subjects) (12)	ca. 100	ca. 100	2	0	
H. Friedrich (13)	ca. 200	?	?	53	22.64
Wiese (19) (children as subjects)	ca. 20	10	ca. 60	7	ca. 12

† Nineteen per cent inactive cases.

* These sera reactions were made in Wassermann's Institute.

consideration of the high price of the antigen. The test was always done with one-half of the anticomplementary unit, using the antisheep system. The antigen was found to vary greatly in anticomplementary value, the unit for the test being from 0.05 to 0.01 cc. Its antigenic strength, however, did not parallel its anticomplementary power; thus some ampules which gave a poor titration had to be discarded. In accordance with Schlossberger it was found that the bacillary powder without the addition of lecithin often deviates complement with tuberculous serum, although less frequently than the lecithinized extract.

Six hundred and forty-six patients were examined. In table 2 our tuberculosis patients are tabulated according to their clinical diagnosis.

The high percentage of negative reactions in the group of incipient and moderately advanced cases shows that this reaction is not of great diagnostic value. Unfortunately, we were not given the opportunity to examine a large number of inactive patients; but even our small number shows that complement fixation with Wassermann's antigen (as with any other one) indicates infection but not disease.

It was not possible to ascertain any prognostic significance of this reaction from these studies; neither did the strength of the fixation have any bearing on prognosis. It is for obvious reasons not permissible to deduce, from the fact of the higher percentage of positives in the far-advanced cases compared to the incipient ones, the theory that

TABLE 2

Tuberculosis patients

CLINICAL DIAGNOSIS	NUMBER OF CASES	PERCENTAGE OF NEGATIVE REACTIONS
1. Undoubtedly active tuberculosis	396	28.5
Incipient	61	37.7
Moderately advanced	106	30.2
Far advanced	225	25.3
Pleurisy	4	25.0
2. Arrested	14	57.2
3. "Suspected tuberculosis"	17	17.7
4. Lymph-node tuberculosis	82	42.6

a positive test is prognostically unfavorable. On the other hand Wassermann's explanation for negative results in active cases cannot be valid throughout, as is evidenced by our large percentage of negative tests in incipient and moderately advanced patients.

The nontuberculous patients examined are listed in table 3.

Like those of most of the previous investigators, our studies did not substantiate Wassermann's claim of absolute specificity of his antigen. All the positive reactions reported in this table were only + or ++; if, however, all + and ++ reactions were to be disregarded, the percentage of positive fixations in active cases would not be more than about 30 per cent. The findings did not reveal a pronounced tendency of this antigen to cross-fixation with syphilitic sera. Forty-eight sera with a positive Wassermann test (Kolmer's technique) and negative

tuberculosis complement-fixation were observed. The serum of pregnant women, however, evidences a definite tendency to nonspecific fixation. The sera of 17 rabbits were examined; 5 were anticomplementary, and 8 gave positive fixations. Three of the latter rabbits died shortly after the test had been performed, and were thoroughly examined, but no evidence of tuberculosis could be found.

TABLE 3

Nontuberculous patients

CLINICAL DIAGNOSIS	NUMBER OF CASES	NUMBER OF POSITIVE REACTIONS
1. Nontuberculous lung conditions	17	
Lung abscess		2
Pneumonia		1
2. Clinical syphilis	12	
Pulmonary syphilis		1
Cerebrospinal syphilis		2
Gummata of pharynx		1
3. Chronic and acute infections	26	
Gonorrheal stricture of urethra		1
Cystitis		1
Typhoid fever		1
Catarrhal jaundice		1
Influenza		1
4. Cardiorenal conditions	11	
Cardiorenal decompensation		1
Pericarditis		1
5. Malignant tumor	3	0
6. Pernicious anemia	1	0
7. Cirrhosis of liver	1	0
8. Ulcer of stomach	2	0
9. Women shortly before or after confinement	31	12
10. Psychic cases	7	0
11. Normals	25	
Newborn with negative Pirquet test		1
Total	136	27

DISCUSSION

Wassermann's claim that deviation of complement with his antigen indicates with certainty absorption of tuberculous material, that is, an active tuberculous process, was not substantiated in our examinations. In a later publication Wassermann (15) made his claim still more definite than in his first paper, even to the extent of the statement

that in case of disagreement between clinical and serological diagnosis the latter must be accepted as truth in analogy to a clinically normal but seropositive syphilitic patient. Although one may agree with Petroff's (16) viewpoint that complement fixation in tuberculosis is a strictly specific reaction, there has been no conclusive proof as yet that complement deviation with any antigen, including the one under discussion, indicates tuberculous *disease* as distinguished from tuberculous *infection*. Granted that some of our patients reported as nontuberculous may have an unrevealed active process, it is certainly not true of all of them. Especially the women, shortly before or after confinement, have been under careful observation for some time following their confinement, and no sign of tuberculosis has developed. All these cases and the ones of arrested tuberculosis may be specific reactions against a tuberculous infection without an active disease. But the case of the newborn, who had a negative Pirquet test, must obviously be listed as a nonspecific reaction. The same is to be said of the three rabbits mentioned above. Whether the lecithin (the only nonspecific substance in Wassermann's antigen) is the cause of these nonspecific fixations is not yet determined.

Considering the fact that the percentage of positive fixations is, roughly speaking, about the same with the majority of antigens so far tested, it appears to us that this limitation is due less to the quality of the antigen than to the biological character of the disease. We believe that our findings substantiate again the teachings of Much (17) (18) that the humoral antibodies in tuberculosis are inconstant, that their presence or absence is no indication of the state of immunity, and that they are of very limited diagnostic value and of no prognostic significance at all.

SUMMARY AND CONCLUSIONS

1. Wassermann's new antigen for complement fixation in tuberculosis has been applied to the serum of 646 patients, and was found to react in 71.5 per cent of active tuberculosis. It also reacted with the serum of clinically arrested patients and a number of clinically nontuberculous patients.

2. This antigen has a definite tendency to give nonspecific fixation with serum of women shortly before or after confinement.

3. Complement fixation with Wassermann's antigen has limited diagnostic value and no prognostic significance.

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A STUDY OF THE NATURE OF THE SPECIFIC SUBSTANCES IN BROTH-CULTURE FILTRATES OF TUBERCLE BACILLI[1]

L. DIENES AND E. W. SCHOENHEIT

The chemical nature of the specific substances contained in the filtrates of tubercle-bacillus cultures has not yet been decided, but there is strong evidence that they are of protein nature, as was originally supposed by Koch. For the literature we may refer the reader to the summary given by Long (1). A great lack in the investigations is that the strength of the filtrates and the probable amount of protein present in them have usually not been determined. The smallest amount of unchanged protein of the tubercle bacillus which gives a markedly positive reaction in moderately sensitive guinea pigs is, according to our estimation, 0.001 mgm., and with very sensitive guinea pigs or human beings a small fraction (less than 1/100) of this. This amount must not show the ordinary reactions of proteins even when concentrated ten times.

We find certain facts described in recent publications of Michealis and Davidsohn (2) and Gabbe (3) to be of great interest. Michealis describes a method of purification of old tuberculin, which consists in the precipitation of the specific substance with acid precipitation at a certain pH concentration. Gabbe, determining the isoelectric point of specific protein substances contained in the old tuberculin, found it the same as the proteins extracted by a certain method from the tubercle bacillus. This is not a proof of the identity of the two substances, but it contains much evidence of it.

For the further elucidation of the question of the chemical nature of specific substances contained in the broth filtrates of tubercle bacilli, we shall describe two observations. We shall show by the method followed in the former paper that, after precipitation with acetic acid and heating, only a small percentage of the specific substances of the filtrate remains in solution. Then we shall show that the specific substances precipitated from the culture filtrate build antibodies in the

[1] From the von Ruck Research Laboratory for Tuberculosis, Asheville, North Carolina.

animal body in the same way as do the protein substances of the tubercle bacillus. If the culture filtrate was first heated in the water-bath no antibodies were formed. The last observation should inform us that the known property of old tuberculin not to be able to induce the formation of antibodies, or produce anaphylaxis in moderate amount, is due to the heating and not to the absence of protein substances.

The question of the antibody formation with old tuberculin, which seems to be not without importance, as far as the literature is known to us, has not been settled. The bouillon filtrates have not been examined (we were not able to find any data in the literature covering this), and with the investigations made with old tuberculin mainly guinea pigs were used, which do not easily form antibodies. The conclusion generally drawn is that old tuberculin has no antigenic properties comparable to the usual antigenic properties of protein substances. This is the opinion of Bandelier and Roepke (4) who connect it with all tubercle-bacillus preparations, as a conclusion from the observations of Ruppel and Joseph which have since been contradicted.

Selter (5) regards old tuberculin as a pure irritant without antigenic properties. Zinsser (6) cites the view of Landsteiner regarding the tuberculin, founded on its incapacity to form antibodies. The examination of artificially changed products as they are in old tuberculin, however important it may be for the elucidation of certain problems, seems to us not as important as the examination of native products, from the properties of which the unusual properties of the changed products are to be understood.

EXPERIMENTAL

The precipitation of the bouillon filtrate, for the examination of its effect on the amount of antigens remaining in solution, was made in the same way as described in the previous paper from our laboratory; adding acetic acid until the best precipitation occurs, then heating 30 minutes in boiling water-bath, centrifugating and neutralizing. As the bouillon contains other protein substances besides the bacillary proteins, we cannot expect as good precipitation as in the watery extract or in a protein solution.

According to table 1 the precipitation destroys nearly all the antigenic properties of the bouillon filtrate in complement fixation, and reduces considerably its potency in skin testing (to one-eighth of the original value). Inasmuch as this reduction does not go as far as it does with

the watery or NaOH extracts, it seems conceivable to us that the precipitation is not so complete as by them. We cannot decide whether or not any significance is to be attributed to the fact that the lowering of the two immunological properties does not run closely parallel. Both of them are exposed to so many influences.

We know from former studies that considerable amounts of protein substances of tubercle bacilli are necessary to induce the production of antibodies. For the concentration of bacillary products and the separation of them from the bulk of the substances contained in the bouillon, we used the property of the bacillary product to be precipitated with acetic or hydrochloric acid. The acids produced precipitates in several samples of broth before the culturing of the bacillus, and in all of those which we examined we found quite an abundant precipitate after their growth. The precipitate after dissolution in weak NaOH contains one-fourth of the antigen potency of the filtrate measured by comple-

TABLE 1

	AMOUNT NEEDED FOR COMPLEMENT FIXATION	AMOUNT NEEDED FOR SKIN TEST
	cc.	*cc.*
Culture filtrate	0.002	0.006
Culture filtrate after precipitation with acetic acid and heating	0.25	0.05

ment fixation, and the solution used for the treatment of animals was four times as potent as the original filtrate. The precipitate from the heated filtrate contained only one-fifteenth of the original strength of the filtrate.

Several 3 per cent glycerol-broth, four weeks' old cultures of two slowly growing tubercle strains of human type (HD and HA), of medium virulence, were filtered through two layers of filter paper with some paper pulp between them. The perfectly clear filtrate was divided into two parts, one of which was heated ten hours in a boiling water-bath; then both portions were precipitated by adding sufficient 10 per cent acetic acid to produce the maximum precipitation. After 30 minutes they were centrifugated, the precipitate dissolved in the presence of phenol-red with 3/n NaOH, so that the pH of the fluid was never over 7.6 pH. The content of dry material of the solution was determined, and rabbits injected with the same amount of dry material of the precipitate of heated and nonheated culture filtrate. Two prep-

arations were made, the first from 750 cc., the second from 900 cc. of culture filtrate. In the first, heating formed a flocculent precipitation which was discarded; in the second no precipitation was formed. The solutions were preserved by the addition of chloroform which excluded the presence of even small numbers of living tubercle bacilli.

Three rabbits (109, 110, 111) received from May 22 to May 30, at four-day intervals, 2, 4 and 8 mgm. of the nonheated, and three rabbits (112, 113, 114) the same amount of the heated precipitate. From June 27 to July 1 they again received 12 mgm. in 2 injections. Rabbit 110 died June 6 of an intercurrent disease. As table 2 shows, the nonheated precipitate induces very strongly the formation of antibodies; the heated, after five repeated injections, did not form any. It cannot

TABLE 2

NUMBER OF RABBIT	TREATED WITH	TITRE OF BLOOD SERUM TAKEN ON JUNE 7	TITRE OF BLOOD SERUM TAKEN ON JULY 8
109	Acid precipitate of nonheated culture filtrate	1:40 ++++	Died
110	Acid precipitate of nonheated culture filtrate	1:40 ++++	1:160 +++−
111	Acid precipitate of nonheated culture filtrate	1:40 +++−	1:160 ++−−
112	Acid precipitate of heated culture filtrate	1:10 +−−−	1:20 ++−−*
113	Acid precipitate of heated culture filtrate	1:10 −−−−	1:10 +−−−
114	Acid precipitate of heated culture filtrate	1:10 ±−−−	1:10 −−−−

* Serum control 1:5 ++−−.

be decided with certainty whether or not the substances able to produce antibodies in the animal body are necessarily protein substances. But the observation that the specific substances are precipitated from the culture filtrate of the tubercle bacillus under the same conditions as the proteins of the tubercle bacillus are, and only a small part of them remain in solution, and the observation that they build in the animal body the same antibodies as the protein substances of the bacilli, furnish strong evidence to indicate that the major part of the specific substances yet demonstrated in the filtrates are the same as those connected with the protein substances of the bacilli. We have to attribute the inability of old tuberculin to build antibodies to the injuries suffered by it during the heating.

SUMMARY

It is shown that the specific substances of the filtrates of broth cultures of the tubercle bacillus are precipitated in the same way from the filtrates as the protein substances contained in the watery extracts of the tubercle bacillus. The precipitated specific substances build the same antibodies in the noninfected animal body as the bacillary protein substances do. This forms further evidence that the specific substances of the broth filtrates are of protein nature.

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THE CHEMICAL COMPOSITION AND ANTIGENIC PROPERTIES OF THE TUBERCLE BACILLUS[1]

L. DIENES, E. W. SCHOENHEIT AND L. D. SCHEFF

The chemical composition of the tubercle bacillus has been the subject of extensive investigation, but so far as we know, with the exception of the work of Behring (1), who made only a short communication on this subject, no systematic effort has been made to study the immunological properties of the different chemical constituents of it. Behring gives the average values of the potency, as measured on tuberculous cattle, of culture filtrates, of different bacillary emulsions and of proteins precipitated from the watery and sodium-hydroxide extracts of tubercle bacilli, and of some other substances (tuberculothymic acid, tuberculosamine), to which he attributes great importance for the understanding of the specific effect of tubercle-bacillus preparations. He states too that none of his preparations have any value in preventive immunization. As he gave only average values and was preoccupied with the significance of tuberculothymic acid, further examination of the distribution of the tuberculin effect on the substances of the bacillary body is not superfluous. Ruppel and Rickmann (2) recommend the use of a tubercle-bacillus serum for the estimation of the specific substances of the tubercle bacillus with complement fixation. In their publication there is given only the results of examinations of three preparations (bacillary emulsion and Koch's O.T. and T.R.), which they find related to one gramme of dry material of equal potency. They do not compare the potency so determined with effects on tuberculous animals.

The extensive literature on the use of different antigens for the complement-fixation reaction for tuberculosis contains much valuable data concerning the properties and strength of antigens, but is not in direct connection with our subject.

No agreement has been reached concerning the chemical nature of the substances to which the bouillon filtrate of tubercle-bacilli cultures

[1] From the von Ruck Research Laboratory for Tuberculosis, Asheville, North Carolina.

and old tuberculin owe their specific activity, although their protein nature is made probable.

Of greatest interest is the distinction made by Zinsser (3) between the antigens of protein nature and other antigens, probably nonprotein, which are resistant to heat, diffusible and connected with the true skin reaction in tuberculosis and some other diseases. The chemical nature and eventual derivation of the residual antigen from the proteins, according to Zinsser, remain undecided.

The following investigation is the first part of a systematic inquiry into the immunological properties of the different substances which we can isolate from the tubercle bacillus. The investigation in its present shape has not passed the preliminary stage, but we believe it appropriate to give an account of it. We have tried to pay as much attention as possible to the quantitative side of the question, and it seems that the only conclusions we can draw have been thus obtained. In this paper we shall treat only of the protein substances of the tubercle bacillus in their relation to the skin reaction in sensitive animals, and their function as antigens in complement fixation. We selected these two properties because they seem to represent the two most divergent phases of antigen function (not taking into consideration the immunizing properties), and both of them can be examined with dissolved as well as with corpuscular, suspended material. After a description of experimental material, we shall treat of the limitations of the method and the conclusions which they allow. In the preparation of the substances examined we used methods which influence, as little as possible, immunological properties, and tried to control such influences.

EXPERIMENTAL

Carefully defatted tubercle bacilli were extracted first, twice with distilled water, then twice with a weak NaOH solution. From the extract the protein substances were obtained either through precipitation with sodium sulphate, or with acid and heating. The following preparations were obtained and compared as antigens: Dried tubercle bacilli extracted with ether and alcohol, suspended and ground in distilled water; living tubercle bacilli; the clear filtrate of the first mentioned suspension (watery extract); the sodium-sulphate precipitate of the watery extract and the filtrate after the precipitation; the filtrate after precipitation with acetic acid, sodium chloride and heating of the

water extract; extracts with 0.02, 0.2 and 1 per cent sodium-hydroxide solution of the bacilli previously extracted with distilled water; the precipitate with acetic acid and the filtrate from the precipitate of the sodium-hydroxide extracts; and the residue of the sodium-hydroxide extraction.

These preparations were made as follows: Four-weeks-old glycerine-bouillon cultures of a human strain (*D*) of medium virulence were dried *in vacuo* over sulphuric acid, then extracted under continuous grinding, twice with water-free ether (48 hours) and twice with water-free alcohol (24 hours). The bacillary mass, after evaporation of the large part of alcohol, was ground three days with distilled water with the addition of 0.3 per cent of chloroform. This constitutes the bacillary emulsion. This emulsion was filtered first through filter paper in a Buchner funnel, which gave, after a certain amount had gone through, a nearly clear filtrate. This filtrate was again sent through a paper-pulp filter, which gave a perfectly transparent filtrate. The watery extract was precipitated at 37°C. with anhydrous sodium sulphate until saturation, and the precipitate pressed out on a clay plate and dried over sulphuric acid. The filtrate, cooled in the refrigerator, filtered off from the sodium-sulphate crystals, evaporated again over sulphuric acid until crystallization began, and cooled again, was freed of the bulk of the sodium sulphate.

The watery extract was precipitated with acetic acid which was added until a good flocculation occurred; then 1 per cent sodium chloride was added and it was heated in the boiling water-bath for 30 minutes; after a few hours it was centrifugated, the perfectly clear supernatant fluid nearly neutralized, again heated and kept overnight. Sometimes a few flakes were formed by standing. The clear fluid was not filtered through a Berkefeld or other filters.

The residue of the bacillary emulsion, after the filtering off of the watery extract, was extracted again with distilled water while being ground for two days, filtered off, and the residue used for sodium-hydroxide extraction. This extraction with sodium-hydroxide solutions was made during the night with grinding. The next morning, without neutralization, it was filtered through paper in a Buchner funnel, which gave a perfectly clear filtrate. The filtrate was neutralized approximately 24 hours after the beginning of the extraction. The sodium-hydroxide extract was precipitated without heating, but with enough acid added slowly so that the best flocculation resulted. Then 1 per

cent sodium chloride was added and heated for 30 minutes in the boiling water-bath.

The residue of the sodium-hydroxide extraction was extracted in the same way as above described, the second time with sodium-hydroxide solution, and, after filtration, washed several times with distilled water.

In one instance, starting with 14 gm. dried bacilli of a young culture of a fast growing strain, only 22 per cent of the defatted bacilli remained undissolved, 54 per cent going into solution with distilled water and 23 per cent with 0.5 per cent sodium-hydroxide solution. The residue after sodium-hydroxide extraction contained 45 per cent ash and only 1.6 per cent nitrogen. The dried material of the watery extract contained 4.6 per cent nitrogen and 12 per cent heat-coagulable protein. The sodium-hydroxide extract contained 11.5 per cent nitrogen. Usually we obtained, from a four to six-weeks-old culture of slowly growing virulent bacilli, 30 per cent of defatted dry material by solution with distilled water with 7 to 12 per cent coagulable protein; and 25 per cent through two extractions, each of 24 hours, with 0.2 per cent sodium-hydroxide solution with about 60 per cent coagulable protein. A prolonged extraction with more concentrated sodium hydroxide (1 per cent) gives considerably more extract (35 to 40 per cent), but the extract is nearly ineffective as antigen and it evidently changes in its properties.

The substance to which we refer as coagulable protein, from both watery and sodium-hydroxide extract, is precipitated nearly completely by adding carefully acetic or hydrochloric acid to the tubercle-bacilli extracts until the best flocculation occurs. It is precipitated by boiling in the presence of acetic acid and sodium chloride. This substance is identical to the protein of the tubercle bacillus found by the first investigator, Hammerschlag, and since then studied several times. We are unable to decide whether the protein substance of the watery and sodium-hydroxide extracts are identical or different. Both of them have nearly the same nitrogen content (calculated on the ash-free material at 13.2 and 12.9 per cent). The phosphorus content of the protein from the watery extract was 2.2 per cent, which was not changed after dissolving three times with sodium hydroxide and precipitating with hydrochloric acid. The phosphorus content of the protein from the sodium-hydroxide extract was 1 per cent. But the high ash content of the preparations (9.9 and 8.4 per cent), from which we were not able to free them without destroying their immunological properties,

prevents our drawing any conclusions according to the difference of phosphorus content. The dissolving with weak sodium hydroxide solution and precipitation with acetic acid, repeated three times, lowered the antigenic value of the preparation in complement fixation to one-tenth of its original value.

In the watery and sodium-hydroxide extract precipitated with acetic acid and heat, as described above, small amounts of proteins can remain. That this method is not good for the precipitation of the last traces of proteins is known from experience with the deproteinization of blood, and it has been newly emphasized by Zinsser (4) that the remaining small traces are enough to show immunological reactions. We tried to avoid this difficulty by using quantitative methods in the determination of immunological properties of the filtrate. As the determination of a very small amount of protein is quite difficult in the presence of proteoses and other nitrogen compounds, we tried to determine the amount of portein remaining in solution after precipitating the purified proteins. The solution after the third, fourth and fifth subsequent precipitations contained, as smallest amount, 0.04 mgm. organic material in 1 cc., with about 13 per cent N, 50 per cent C, and 1.5 per cent P.[2] The composition corresponds to that of protein and with the analysis our purpose was to exclude the presence of carbohydrates. It seems to us that the substances remaining in solution are proteins, as nearly decided by the fact that the filtrates gave a faint turbidity by saturation with sodium sulphate or ammonium sulphate, and that precipitation with sodium sulphate removes all demonstrable traces of antigens from the filtrates. From the original extracts the precipitation of protein probably is not as good as from the solution of purified substances. We judge it more advisable not to perform filtration through Berkefeld filters because the amount of floating substances in a clear fluid is very small (in a bacterial emulsion a few thousandths of a milligram of dry material in 1 cc. can be noticed), and on the other hand dissolved substances can be absorbed during the filtration.

The examination of the tuberculin effect of the preparation was made on tuberculous guinea pigs which received 8 to 10 injections in both sides of the body. Dilutions of the same watery extract together with the examined substance were injected into every animal to make the

[2] For the chemical work we used a microbalance of 0.001 mgm. sensitivity, and analyses were made according to methods adapted to the determination of the smallest quantities. Until now only the description of phosphorus determination has been published (5).

determinations on different animals comparable. The method of giving multiple injections is recommended, for instance by Loewenstein (6), for the elimination of differences of sensitiveness of the animals. For the titration of the preparations we diminished to one-half at each injection the amount injected. It seems to us that, proceeding in this way, the error will rarely be higher than 30 to 40 per cent. The use of

TABLE 1

	CONTENT OF DRY ORGANIC MATERIAL	COAGULABLE PROTEIN CONTENT OF THE DRY ORGANIC MATERIAL	NITROGEN CONTENT OF THE DRY ORGANIC MATERIAL	MINIMUM AMOUNT GIVING FIXATION COMPLEMENT WITH TUBERCULOSIS SERUM	MINIMUM AMOUNT GIVING SKIN TEST ON TUBERCULOUS GUINEA PIGS
	per cent	*per cent*	*per cent*	*mgm.*	*mgm.*
Living tubercle bacilli					0.006
Emulsion I of defatted tubercle bacilli ground with distilled water 3 days (March, 1923)	5.9		7.75	0.003	0.006
Filtrate of the above emulsion	2.3		4.5	0.045	0.045
The same filtrate after one year	2.3	1.6	4.5	0.092 (0.0015*)	0.092 (0.0015*)
1 per cent NaOH extract, extracted 3 days	2.7	37.0	10.0	0.25†	0.1
Remainder after 2 NaOH extractions (1 per cent NaOH)	4.3		6.1	0.006	0.012
Emulsion II of defatted tubercle bacilli made as emulsion I (March, 1924)	4.6		8.8	0.004	0.006
Filtrate of emulsion II	1.0	11.0	7.0	0.016 (0.0018*)	0.022 (0.0024*)
Na_2SO_4 precipitate of Filtrate II		over 90.0	12.0	0.003	0.0032
Filtrate II after Na_2SO_4 precipitation				0.7‡	2.0§

* Protein.
† No reaction.
‡ Checking in itself.
§ Slight reaction.

moderately sensitive animals seems to be preferable to very sensitive ones. The antigen content of the preparations in the complement-fixation experiment was titrated, using the same amount of serum and complement (of the complement 2 units), and diminishing with each tube to half the amount of the antigen. We used rabbit sera of high titre, as concentrated as possible, and we used 2 to 3 serum dilutions

with each dose of antigen. To eliminate the varying influences of the experiment, in every titration the same watery extract was run parallel. The error by our estimation is not higher than 30 to 40 per cent.

Tables 1 and 2 contain the description of the main chemical properties of the substances examined, and their potency as antigens in complement fixation and in skin tests.

Examining tables 1 and 2, the first significant thing is a quite close parallelism between the potency of the preparations in the two antigenic properties. The difference of proportional effectiveness, in the com-

TABLE 2

	CONTENT OF DRY ORGANIC MATERIAL	COAGULABLE PROTEIN CONTENT OF DRY ORGANIC MATERIAL	MINIMUM AMOUNT GIVING COMPLEMENT FIXATION WITH TUBERCULOSIS SERUM	MINIMUM AMOUNT GIVING SKIN TEST ON TUBERCULOUS GUINEA PIGS
	per cent	*per cent*	*mgm.*	*mgm.*
0.02 per cent NaOH extract of defatted tubercle bacilli formerly extracted with distilled water	0.12	51	0.0024 (0.0012*)	0.0036 (0.0018*)
0.2 per cent NaOH extract	0.40	60	0.006 (0.0036*)	0.006 (0.0036*)
1 per cent NaOH extract	0.78	36.5	0.012 (0.0042*)	0.013 (0.0045*)
Second extract with 0.2 per cent NaOH	0.27		0.05	0.026

* Protein.

plement-fixation and skin tests, of the emulsion and watery extract I of March, 1923, and those (II) of March, 1924, is probably only apparent, because in the skin test we have had no common measure for comparison, and the watery extract of March, 1923, evidently lost a large part of its effectiveness by the time of the preparation of the other extract. The most effective was the dry material of the 0.02 per cent sodium-hydroxide extract (of bacilli formerly extracted by water). The parallelism of two such different properties, even in substances not purified, adds some probability to the supposition that they are connected with the same substance.

The potency of the two preparations is very much the same if we do not calculate it in the proportion of dry material, but of the coagulable protein contained in them.

Then we found 0.0012 mgm. in the 0.02 per cent sodium-hydroxide extract correspond to 0.0015 and 0.0018 in the watery extracts. These values would be quite in agreement with 0.003 to 0.004 mgm. in the emulsions, which, based on their nitrogen content, contains quite a large amount of nonprotein substances. Unfortunately, in the watery extract I of March, 1923, the content of coagulable proteins was only determined one year after it was obtained, when its potency had fallen to one-half of the original value. The filtrate originally must have contained more proteins, but according to its low nitrogen content, less than is usually found in the watery extract.

To judge the significance of the correspondence and variations found in table 1, it is important to know that the potency of the preparations is very variable, according to the condition of the preparation. As we may see in table 2, raising the concentration of sodium hydroxide from 0.02 to 0.2 and 1 per cent, the potency of the preparations, calculated for the protein content, is lowered from 0.0012 to 0.0036 and 0.0042 mgm. The precipitate with acetic acid and solution with 0.03 normal sodium hydroxide, repeated three times, lowered the potency of an acid precipitate of the watery extract, as mentioned before, to one-tenth of its original value, and the loss could not be found in the solution from which the precipitation was made. In the watery extract precipitated with sodium sulphate no antigens were demonstrable, notwithstanding the fact that, in the precipitate which can be dissolved only with sodium hydroxide, the protein substances have a potency of only one-half of the potency of watery extract calculated in proportion to the protein substances. If the effect of sodium hydroxide is more prolonged, nearly all the potency of the preparation is destroyed. In table 2, the extract with 1 per cent sodium hydroxide was neutralized after 24 hours. In an extract with 1 per cent sodium hydroxide (table 1) which was neutralized only after three days, nearly all potency disappeared. It seems that the potency measured with the skin test is more stable than the potency measured by complement fixation. In the sodium-hydroxide extracts, except that with 0.02 per cent sodium hydroxide, and visible in the second sodium-hydroxide extract, the potency in the skin test is relatively higher than in complement fixation.

In contrast to the influence of alkalinity the influence of heating is

less. A weak solution of protein and a suspension of bacilli heated 20 minutes in the boiling water-bath, as shown in table 3, did not lose any of their potency.

The observation seems to be of importance that different sera, used approximately in the same proportion and titre, lead approximately to the same results as regards the antigenic value of the different prepara-

TABLE 3

Minimum amount for complement fixation with different tuberculosis sera, of an emulsion of tubercle bacilli, of a watery extract, and of the remainder after NaOH extraction

	EMULSION I	WATERY EXTRACT I	REMAINDER AFTER NaOH EXTRACTION
Serum 9	0.003	0.045	
Serum 50	0.0035	0.04	0.006
Serum 81	0.003	0.045	0.006
Serum 52	0.015*	0.04	0.006

* Higher dilutions not examined.

TABLE 4

	MINIMUM AMOUNT GIVING COMPLEMENT FIXATION WITH TUBERCULOSIS SERA	MINIMUM AMOUNT GIVING SKIN TEST IN TUBERCULOUS GUINEA PIG
	cc.	*cc.*
0.2 per cent NaOH extract	0.002	0.004
The same extract precipitated with acetic acid, precipitate suspended in normal saline (in the same amount as the extract):		
Nonheated	0.004	0.007
Heated	0.004	0.007
Suspension dissolved in NaOH (nonheated)	0.010	*
Filtrate of the above precipitate:		
Nonheated	0.04	0.04
Heated	0.04	0.04

* Not determined.

tions. This is the case also with our serum 52, which, as described in a former publication (7), has no affinity for the lipoids of the bacteria. This shows that the antigenic value of the bacillary emulsion and of the residue of the sodium-hydroxide emulsion is not derived from any lipoid remaining in them but from proteins contained in them.

From this part of our investigations we draw the conclusion that there is a rough parallelism between the potency of the preparations in the skin test and complement fixation, and between them and their

content of coagulable protein. A close examination of this relationship is made very difficult by the great sensitiveness of the preparations.

From the foregoing statement we shall not conclude as to the chemical nature of the bearer of the antigenic properties. We tried to characterize these more closely, mostly influenced by the conception of Zinsser of the residue antigens, by examining the effect of removal of proteins from the solution. In table 5 is given an account of an experiment with the watery and NaOH extracts. In both cases after the removal of protein with acetic acid and heat, there remains only a small percentage of the former potency in the filtrate, both for complement fixation and the skin test. We have shown above that this is not the result of heating. We pointed out formerly that the method used for the removing of proteins leaves traces of them in solution. After our experience

TABLE 5

	MINIMUM AMOUNT GIVING COMPLEMENT FIXATION WITH TUBERCULOSIS SERA	MINIMUM AMOUNT GIVING SKIN TEST WITH TUBERCULOUS GUINEA PIG
	cc.	*cc.*
Watery extract	0.002	0.002
Watery extract after precipitation with acetic acid and heating	0.08*	0.036†
0.2 per cent NaOH extract	0.002	0.0015
The same extract after precipitation with acetic acid and heating	0.12*	0.05†

* Gives no reaction.

† Reaction less than in former test.

with purified protein, 0.04 mgm. in 1 cc. (0.004 per cent) easily remains in solution, which amount, if active, explains the reaction we found in 0.036 and 0.05 cc. of the filtrates. The filtrate of protein solution, the chemical examination of which we have given, did not show any trace of antigenic properties. Some filtrates made in the same way, although we have not examined them chemically, have shown 1/50 to 1/100 of the original strength, which corresponds to the loss of strength experienced with the watery and sodium-hydroxide extracts.

These experiments do not indicate that we have the right to suppose the presence of other antigens than the proteins in the extract. The rough parallelism in the decrease of the potency for the complement-fixation and skin tests (we cannot expect more than a rough parallelism) is also against this supposition. The presence of antigens other than

proteins could be proved only if the extract, after precipitation, would show antigenic properties which cannot be explained by the traces of protein present, and by the injury suffered by them during their preparation. On the other hand, the presence of antigens of different nature than proteins, even in such small quantities that they cannot be noticed with our rough quantitative methods, can have the greatest significance for the pathology and immunity of the disease; and we have no convincing proof to show that the protein substances of the tubercle bacillus plays the deciding rôle.

We have to come back to the question of how well are the immunilogical methods used by us adapted for quantitative comparison. With substances in solution it seems to be accepted that dilutions showing the same antigenic strength contain the same amount of a supposed antigen. But on close examination it seems that the parallelism of effect and amount even here can have important limitations. The fact that cholesterin enhances the effectiveness of the Wassermann antigen, even taking into consideration that the Wassermann antigen is an emulsion, and it is not even sure that the reaction is a true antibody reaction, indicates that under certain conditions the apparent antigenic value shows great variations. The mechanism of the skin reaction is even less known than that of complement fixation, but the recent observation of Opie on the fixation of antigens at the place of injection shows how many factors enter into it. The sources of error are greater if we compare corpuscular and practically insoluble substances with solutions. We were ourselves impressed by how little the antigenic value of bacillary emulsion is influenced by the more or less fine dispersion of the bacilli, and how regular was the outcome of the exponents. We believe it necessary to lay stress on the fact that our quantitative estimations and the conclusions based on them are exposed eventually to serious errors.

But, even taking into consideration the foregoing difficulties, we were much impressed by how closely connected the protein content of the preparations and the strength of antigenic properties seem to be. In other work from our laboratory it seems to us that quite convincing proofs are at hand to show that the culture filtrate of the tubercle bacillus, the mother substance of old tuberculin, as was originally supposed by Koch, owes its antigenic property to the presence of the same protein. It seems to us that these observations, and the observations that besides the protein substances we were not able to demonstrate the presence

of other antigens, are much in favor of the conception that the hypersensitiveness developed during the disease is a hypersensitiveness against the protein substances of the tubercle bacillus, as much as antibody reactions *in vitro* are connected with them, and quite probably they have an important part in the pathology of the disease. This preliminary conclusion may seem to be a truism. In nearly all cases in which we are able to make suppositions as to the mechanism of the pathological events, except in the case of microörganisms with ectotoxin production, the proteins of endotoxins of the microörganisms are made responsible for them. Many of the conceptions of hypersensitiveness in tuberculosis suppose that it is derived from sensitization with bacillary proteins. And the demonstration of the close connection of hypersensitiveness to proteins in the case of tuberculosis seems to substantiate this conception and make it more clear.

CONCLUSIONS

1. Studying the antigenic strength of various preparations of tubercle bacilli in the complement fixation and in skin tests on tuberculous guinea pigs, a quite close parallelism is found first, between these two properties, and, second, between the content of the preparations in coagulable proteins and their antigen content.

2. In watery and sodium-hydroxide extracts of the bacillus we were not able to confirm the presence of antigens not connected with the proteins of the bacilli.

3. The protein substance of the tubercle bacillus seems to be connected (although these experiments do not contain convincing evidence of it) as much with the hypersensitiveness of tuberculous animals as with their antibody reactions.

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STUDIES IN TUBERCULOSIS

II. A CLINICAL STUDY OF TUBERCULIN REACTIONS WITH NEW DERIVATIVES OF TUBERCULIN[1]

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In earlier experimental studies (1), it was shown that tuberculous animals react to certain new derivatives prepared from tuberculin. Of particular significance were the observations relating to sensitization phenomena in normal animals, the early diagnosis in infected animals, and the noteworthy range of these tuberculin derivatives in detecting bovine as well as human tuberculous infections.

The value of a properly performed skin test in the diagnosis of juvenile tuberculosis has been established beyond doubt. Any differences of opinion which may exist are related rather to the interpretation of the tests than to their significance. When reactions are positive in children under twelve years of age and, more especially in the age groups of less than one year to two years and of two to ten years, there is evidence which points to tuberculosis somewhere. A history, carefully elicited from the clinical as well as from the social aspects of the patient, will strengthen the clinician's suspicions even in the absence of definite auscultatory or other findings, which in juvenile tuberculosis may be negligible or insignificant at best. Where objective signs are present, as in lymph-node tuberculosis or in tuberculosis of the bones or joints, the diagnosis becomes relatively more simple or it may be substantiated with the aid of the X-ray.

There is, however, a great number of little patients who elude a diagnosis, and it is these potential cases of tuberculosis which are most important from the standpoint of prevention and cure of the disease at its very origin. If it can be shown that a more sensitive tuberculin test, performed by cutaneous or intracutaneous techniques, is positive and correlated with other findings of significance, the value of this simple diagnostic procedure will be more fully appreciated. Many children are

[1] This work was done under a grant from the Hennepin County Tuberculosis Association in Minneapolis.

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called "Pirquet negative" solely because of a poor technique in performing the test, which falls far short of the method described by the originator. The customary dispensary or office procedure, as a rule, obviates the use of small pledgets of absorbent cotton over the scarified area and its drop of tuberculin, and disdains a fastening strip of adhesive tape over these. Pirquet's idea was to keep the spot soaked with tuberculin sufficiently long to allow absorption to take place, yet this fundamental step in the technique of the test is generally ignored. Apart from these presumably negative reactors, a large proportion of children does not respond to tuberculins that are now available in the market. Again, the Pirquet method by itself may fail to give aid in the diagnosis of juvenile tuberculosis. A negative test may mean nothing, especially when an intracutaneous test proves to be positive in these same patients. A study of combined cutaneous and intracutaneous tests, and the significance and interpretation of these in juvenile tuberculosis, are reported in another place (2). The present study is a review of the results that were obtained in a series of juvenile cases, in which some new derivatives of tuberculin were being investigated. The main points which have been brought out in this study are as follows:

1: Derivatives of tuberculin are adapted to very early diagnosis of tuberculosis in children, and elicit positive reactions in the face of a negative test with one or another type of ordinary tuberculins.

2: The new preparations of tuberculin are extremely sensitive, and lend support to the clinical picture when the ordinary tuberculin tests fail. Even a slightly positive reaction by cutaneous technique has been found regularly to prove significant in the light of subsequent intracutaneous tests.

3: The derivatives are far more potent, unit for unit, in comparison with ordinary whole tuberculins.

4: The derivatives give reactions that are more clear-cut and persistent, and are of greater severity when a definite focus is present.

5: One of the preparations, *Ether-insoluble X*, possesses remarkable specific properties and gives the sharpest reactions. This derivative is apparently nonprotein in nature, and has the most sensitive and diagnostic range.

6: The clinical findings and the correlated skin tests support the conception that there is an antigenic unit present in specially prepared tuberculin derivatives, and it will detect tuberculosis irrespective of the type of infection.

EXPERIMENTAL

In this series of 50 cases, the *Ether-insoluble X* and *Acetyl* derivatives were studied primarily, and in a limited number the *Benzoyl* preparation was used. Owing to the poorer absorption of the latter as compared with the acetylated material, it was discarded pending newer refinements of preparation. The tuberculin derivatives were prepared according to the method which has been described in another place (1), and their potency at the time when these tests were made had remained unimpaired after eight months. The Pirquet cutaneous method was adopted and controlled simultaneously with ordinary bovine and human Old Tuberculin. To determine more accurately the diagnostic range of the new preparations, a series of intracutaneous tests was also made with varying dilutions of these original tuberculins.

Technique: The flexor surface of the forearm was thoroughly cleansed with 50 per cent alcohol and allowed to dry. A drop of undiluted human tuberculin and of each of the derivatives was placed on one forearm, and a drop of undiluted bovine tuberculin on the other. A globular dental burr of about 1.5 mm. in diameter was used for scarification through the drop with a gentle rotary motion so as to avoid the drawing of blood. Over each area was placed a small piece of sterile absorbent cotton, which was held in place by a narrow strip of adhesive tape. Twenty-four hours later the strips and cotton were removed, and the reactions read. The presence of a definite erythema and induration, with or without umbilication of the lesion, was considered positive, and the extent of this lesion was reported in centimetres. Intracutaneous injections were made with 0.1 cc. of the proper dilutions to effect the desired concentration of the original Old Tuberculin.

SUMMARY OF RESULTS

Forty-five of the 50 cases gave definite positive reactions with tuberculin derivatives. Five negative cases were in a group of out-patients that were tested routinely in a clinic and had no history of exposure, clinical or physical findings. Of this group 2 were tested by the intracutaneous method with the *Ether-insoluble X* preparation and proved negative. Careful X-ray studies revealed no hilum tuberculosis or any evidence of a primary focus. In general, negative reactions of this sort never failed to check up in this manner.

Thirty per cent of the patients reacted more violently or solely to bovine tuberculin, and fell in the age groups of one to five years in half of these cases and between the ages of seven to ten in the remainder. In this group there was no evidence of an adult type of tuberculosis and the findings were chiefly those of tuberculous lymph nodes, bones or joints. The derivatives elicited marked reactions in all of these.

In one instance tuberculin tests, cutaneous as well as intracutaneous, were uniformly negative with ordinary human and bovine tuberculin. The derivatives, however, gave definitely positive reactions. This patient had some cervical adenopathy, and the X-ray showed a primary focus near the right hilum, with enlarged and calcified lymph nodes at the root of both lungs.

A large proportion of the cases reacted more violently or solely to human tuberculin, and responded sharply to cutaneous tests with the derivatives. This group comprised patients between the ages of eight and thirteen years, chiefly, and one of ten months. Here an adult type of tuberculosis was found usually.

The skin reactions with derivatives of tuberculin were uniformly more pronounced than were those with ordinary tuberculins. Without exception it was possible to detect a tuberculous condition whenever the history, clinical picture or X-ray findings served to arouse suspicion, even in the absence of a positive skin reaction with the ordinary preparations.

In 30 per cent of the cases the cutaneous reactions to derivatives of tuberculin were accompanied by lymphangitis with constitutional or focal reactions. The significance of these manifestations will be discussed in separate reports (3) (4). All of these patients exhibited definite juvenile tuberculosis.

INTERPRETATION OF SKIN REACTIONS

In interpreting skin reactions with these tuberculin derivatives it is important to distinguish a pseudo-reaction from a definitely positive one. The former is transitory, and often manifests itself in two phases: first, an immediate erythema of variable extent, without any induration or infiltration, which vanishes within a half-hour or less, and a second reaction which, though similar to the first, may appear within six to eight hours after the test. In both instances the characteristic of this reaction is its evanescence. A positive skin reaction, which is diagnostic, is preceded generally by these pseudo-reactions, but here the criterion is the more marked intensity of the reaction with definite induration or infiltration, its delayed appearance which is usually after 18 to 24 hours, and its relative persistence, with a characteristic residual pigmentation for days or weeks.

Although much stress is laid upon the size of a lesion as a standard whereby to judge a positive reaction, it would appear that this criterion is valueless, for even slightly positive reactions with a more sensitive

diagnostic substance are of utmost significance. Similarly, reactions with ordinary tuberculins, which are usually called negative because they fail to come up to an arbitrarily fixed measurement of so many millimetres, mean a great deal when interpreted in relation to other data in the case. That this contention works out in practice may be seen from our own studies, in which so called doubtful or negligible reactions were destined to be markedly positive when these patients were tested with derivatives of tuberculin.

Every diagnostic procedure has its limitations, and it is imperative that the clinician weigh all of the facts in the case instead of stressing one or two of the equally important established criteria. As an example, roentgenographic chest findings have been exaggerated far beyond the mechanical and human possibilities of the technique, even if one is to assume that the method can reveal every significant bit of pathological changes in the lung and that the roentgenologist's interpretation be correct. There cannot and should not be a divorce between clinical findings, case history and other significant data, and the purely mechanical interpretation of lights and shadows on a plate. In another place these points are developed at greater length and illustrated by clinical material (5).

TYPICAL REACTIONS AND ANALYSES OF CASES

A few of the typical results will be described in some detail and illustrated in order to clarify the discussion of these observations:

Patient C. K.: Male, age five, with the following history: Maternal uncle died of tuberculosis. The child had been fed on cow's milk which was traced to a tuberculous herd. *Physical findings:* Enlarged and suppurating posterior cervical lymph nodes. *X-ray:* Enlarged caseous lymph node at right base; apical pleurisy on right side; enlarged tracheobronchial lymph nodes of right hilum. A diagnosis of tuberculous cervical adenitis was made (fig. 1).

Tuberculin Tests

Method: Pirquet:

Bovine O.T.: 3 × 3 cm., with central zone, 2.5 × 2 cm., and lymphangitis streak 3 cm. long. Marked reddening and infiltration (fig. 2).

Human O.T.: 2.5 × 2.5 cm., with central zone, 1 × 0.75 cm. Moderate reddening and infiltration (fig. 2).

Acetyl derivative: 2 × 2 cm., with lymphangitis streak 4 cm. long and 0.75 cm. wide,—a violent reaction (fig. 5).

Ether-insoluble X: 2.5 × 3 cm., with intense reddening and induration

throughout and lymphangitis streak, 5 cm. long and 1 cm. wide,—a violent reaction (fig. 5).

Method: Intracutaneous:

Bovine O.T.: 1:10,000,000: 1.5 × 1.5 cm., reddened and infiltrated with surrounding erythematous zone. 1:1,000,000: 2.2 × 2 cm., reddened and infiltrated with surrounding erythematous zone. 1:100,000: 3 × 2.5 cm., infiltration and reddening throughout (fig. 4).

Human O.T.: 1:1,000,000: 1.5 × 2 cm., with central zone 0.5 × 0.75. cm. 1:100,000: 3 × 3 cm., with central zone 1.5 × 1.5 cm. 1:10,000: 3.5 × 5.5 cm., with central zone 2 × 2 cm. (fig. 3).

At the height of the tuberculin reactions, the lymph nodes of the neck were markedly increased in size, were reddened, and discharged pus. A sharp rise in temperature accompanied the picture.

Patient M. B.: Female, age four. Mother died of tuberculosis when child was a few weeks old. *Physical findings:* Anterior and posterior cervical adenopathy. *X-ray:* Cervical adenopathy well visualized on left side; very large tracheobronchial gland visualized behind heart shadow on left side, apparently behind second and third ribs. A later picture showed markedly enlarged tracheobronchial gland visualized clearly in the second left interspace behind the second and third ribs; enlarged and calcified hilum glands on right side.

Tuberculin Tests

Method: Pirquet:

Bovine O.T.: 3.5 × 3.2 cm., with lymphangitis streak 3.5 cm. long. Area was markedly indurated and reddened throughout (fig. 6).

Human O.T.: 2.5 × 2 cm., marked reddening and induration (fig. 6).

Acetyl derivative: 1.5 × 1.5 cm., with deep induration and intensely reddened areolar zone 3 × 8 cm.

Ether-insoluble X: 2 × 1.5 cm., with surrounding deep infiltration over area of 2 cm. at periphery of lesion; marked reddening and swelling.

Method: Intracutaneous:

Bovine O.T.: 1:10,000,000: 2.2 × 1.7 cm., with central zone 0.5 × 0.5 cm. and complete induration. 1:2,000,000: 2.4 × 2 cm., with central zone 1 × 1 cm. 1:100,000: 3.5 × 2.5 cm., with central zone 1.5 × 1.5 cm. (fig. 8).

Human O.T.: 1:1,000,000: 1 × 1 cm., with central zone 0.3 × 0.4 cm. 1:100,000: 1.5 × 1.5 cm., with central zone 1 × 1 cm. 1:10,000: 3 × 3 cm., with central zone 1.5 × 1.5 cm. (fig. 7).

As in the preceding case, a constitutional and focal reaction accompanied the tuberculin reactions.

These two cases illustrate a group in which the history, clinical and physical findings, and tuberculin tests suggested juvenile tuberculosis, presumably of bovine origin. The skin reactions in this group were distinctly more positive for bovine tuberculin, as shown especially with the different dilutions, and in several instances were entirely negative to human tuberculin. Despite these limited reactions with ordinary tuberculin preparations the derivatives of tuberculin gave decisive results.

In the following case the diagnostic property of tuberculin derivatives is shown in the presence of a tuberculous peritonitis and kidney tuberculosis.

Patient F. O.: Female, age four and one-half years. The father had died of tuberculosis and the patient had a history of tuberculous cystitis and peritonitis.

Tuberculin Tests

Method: Pirquet:

Bovine O.T.: 3 × 2.5 cm., with marked reddening and induration.

Acetyl derivative: 2 × 1.5 cm., with marked infiltration and erythema.

Ether-insoluble X: 3.5 × 2.5 cm., with marked reddening and infiltration (fig. 9).

Intracutaneous tests in this patient were more pronounced with bovine tuberculin, which gave a positive reaction with a dilution of 1:1,000,000. Human tuberculin elicited a positive reaction in a dilution of 1:10,000.

Patient I. K.: Female, age 19 months. This child had a history of having been fed unboiled milk. The physical findings established a diagnosis of tuberculous dactylitis, involving the second and fourth fingers of both hands. The cervical and inguinal lymph nodes were enlarged, and X-ray of the chest demonstrated an enlarged caseous lymph node at the root of the right lung. The mother of this child is tuberculous.

Tuberculin Tests

Method: Pirquet:

Ether-insoluble X: 4.5 × 2.5 cm., with marked reddening and infiltration over an area of 2 × 2 cm. (fig. 10).

Acetyl derivative: 3.5 × 4 cm., with marked induration and reddening (fig. 10).

Bovine O.T.: 3 × 2.5 cm., with marked infiltration and reddening (fig. 11).

Human O.T.: 2.5 × 1 cm., with reddening and marked infiltration (fig. 11).

Method: Intracutaneous:

Dilution	*Ether-insoluble X*	*Bovine O. T.*	*Human O. T.*
1:1,000,000	1.5 x 1 cm., with marked reddening and induration	1.5 x 1.2 cm., with induration and reddening	1 x 0.75 cm., with reddening and slight induration in centre for an area of 0.2 cm. square
1:100,000			1.5 x 1 cm., with reddening and induration
1:10,000			2.5 x 2 cm., with reddening and induration in centre

This patient reacted sharply to every test, which was accompanied by a constitutional and focal reaction. The intracutaneous tests with diluted tuberculins showed a more pronounced reaction with the bovine type.

In the next case, which concludes this illustrative series, the derivatives of tuberculin elicited marked positive reactions when repeated cutaneous and intracutaneous tests with bovine and human tuberculins had failed. This patient, typical of so many cases of juvenile tuberculosis, presented nothing of a nature definite enough to warrant a diagnosis of tuberculosis, and was kept under observation for over eighteen months.

Patient R. B.: Male, age five years. The mother had died of Addison's disease. Physical findings were negative, except for the presence of enlarged cervical lymph nodes. X-ray showed enlarged and calcified lymph nodes at the root of both lungs and a primary focus at the sternophrenic border on the right side.

FIG. 1. PATIENT C. K. TUBERCULOUS CERVICAL ADENITIS

FIG. 2. PATIENT C. K. PIRQUET TEST

Bovine O. T. (*A*). Human O. T. (*B*). Lymphangitis streak (*SS*).

FIG. 3. PATIENT C. K. INTRACUTANEOUS TEST WITH HUMAN O. T.

Dilutions 1:1,000,000 (*A*). 1:100,000 (*B*). 1:10,000 (*CC*).

FIG. 4. PATIENT C. K. INTRACUTANEOUS TEST WITH BOVINE O. T.

Dilutions 1:10,000,000 (*A*). 1:1,000,000 (*B*). 1:100,000 (C). Note the more extensive lesions as compared with those in fig. 3.

FIG. 5. PATIENT C. K. PIRQUET TEST

Ether-insoluble X substance (*A*). Acetyl derivative (*B*). Lymphangitis streak (*SS*).

FIG. 6. PATIENT M. B. PIRQUET TEST

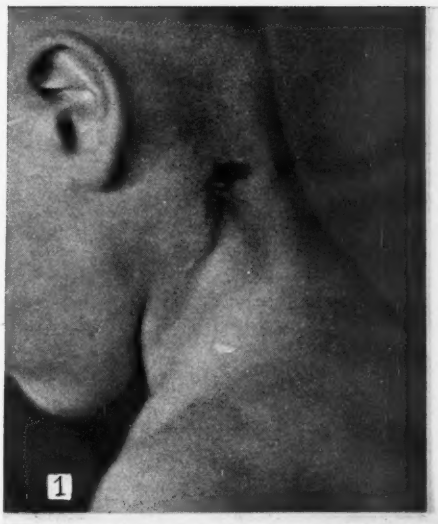
Bovine O. T. (*A*). Human O. T. (*B*). Lymphangitis streak (*SS*).

FIG. 7. PATIENT M. B. INTRACUTANEOUS TEST WITH HUMAN O. T.

Dilutions 1:1,000,000 (*A*). 1:100,000 (*B*). 1:10,000 (*C*).

FIG. 8. PATIENT M. B. INTRACUTANEOUS TEST WITH BOVINE O. T.

Dilutions 1:10,000,000 (*A*). 1:2,000,000 (*B*). 1:100,000 (*C*). Note the more extensive lesions as compared with those in fig. 7.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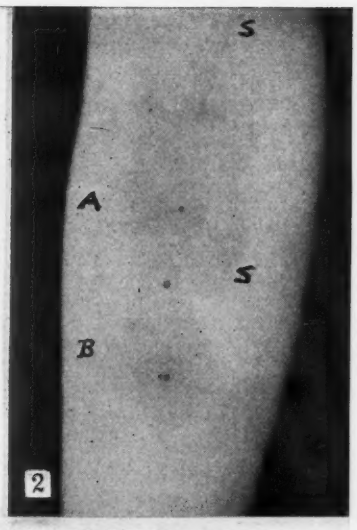
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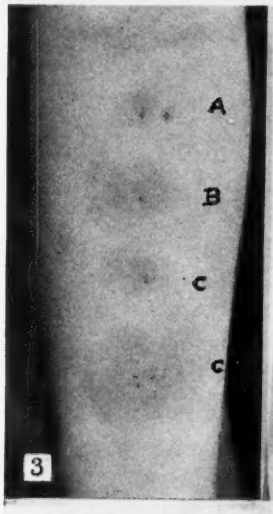
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3

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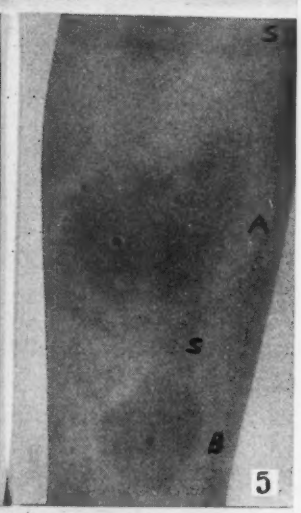
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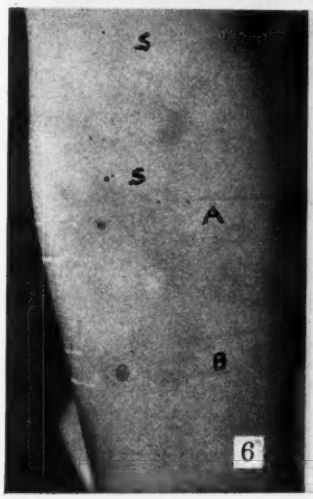
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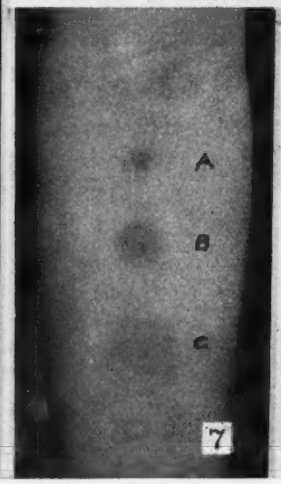
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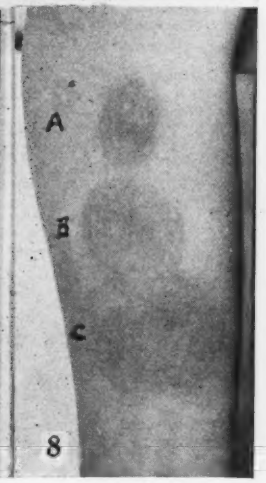
A
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C
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Tuberculin Tests

Method: Pirquet:

Bovine O.T.: Negative.

Human O.T.: Negative.

Acetyl derivative: 1 × 1 cm., with marked reddening and induration (fig. 12).

Benzoyl derivative: 1 × 1 cm., with marked reddening and induration (fig. 13).

Ether-insoluble X: 1.5 × 1.5 cm., with reddening and infiltration (fig. 14).

Method: Intracutaneous:

Dilution	*Bovine O.T.*	*Human O.T.*	*Acetyl Derivative*	*Ether-insoluble X*
1:1,000,000	Negative	Negative		
1:100,000	Negative	Negative		
1:10,000	Negative	Negative		
1:1,000	Negative	Negative		
1:100	Negative	Negative		
1:10	Negative	Negative		
Undiluted	Negative	Negative	Intense reddening and infiltration 2.5 x 2 cm., with erythematous zone of infiltration 4 x 3 cm.	1 x 1 cm., with induration and marked erythema

POTENCY AND CHEMICAL STUDY OF THE TUBERCULIN DERIVATIVES

In connection with the sensitiveness of the preparations which were used in this clinical study, an examination of some of the chemical properties of these derivatives, with special reference to quantitative analysis, is of interest. From the standpoints of actual potency of these preparations and of their standardization such analyses furnish pertinent data.

FIG. 9. PATIENT F. O. PIRQUET TEST

Bovine O. T. (*A*). Acetyl derivative (*B*). Ether-insoluble X substance (*C*).

FIG. 10. PATIENT I. K. PIRQUET TEST

Ether-insoluble X substance (*A*). Acetyl derivative (*B*).

FIG. 11. PATIENT I. K. PIRQUET TEST

Bovine O. T. (*A*). Human O. T. (*B*). Note extent of lesions as compared with those in fig. 10.

FIG. 12. PATIENT R. B. PIRQUET TEST

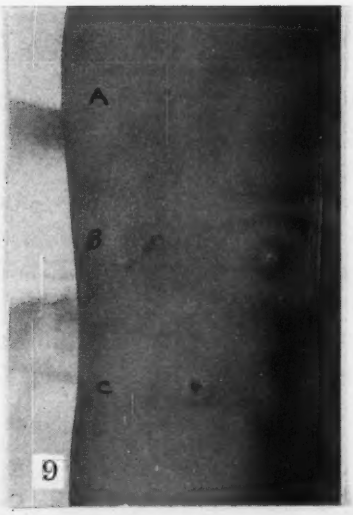
Acetyl derivative

FIG. 13. PATIENT R. B. PIRQUET TEST

Benzoyl derivative

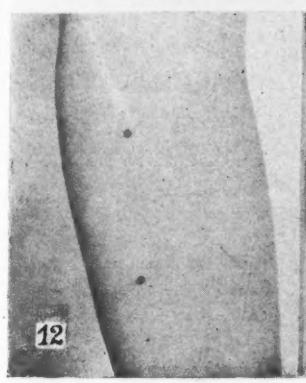
FIG. 14. PATIENT R. B. PIRQUET TEST

Ether-insoluble X substance


A
B
C
9

A
10

11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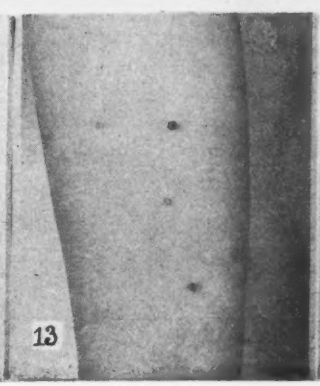
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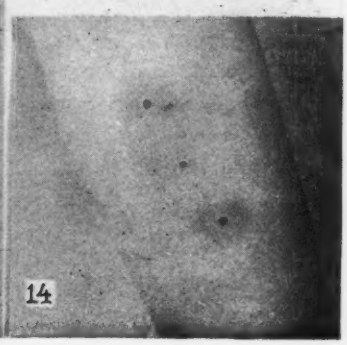
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Reference to the skin tests which have been described in this report will bear out the belief that the derivatives are more effective and specific in the diagnosis of tuberculosis in accordance with our known standards. Unit for unit, the derivatives are doubtless more potent, as a quantitative analysis will show. Given two skin reactions of equal extent and intensity, produced with standardized technique and uniform control by two different test substances, one of which represents a specially prepared fraction of the other, it follows that the more potent of the two materials is the fraction. In these clinical experiments this fact has been brought out regularly. This observation aligns with it the repeated demonstration of more marked reactions in patients who do react to ordinary tuberculins, while of greater significance is the fact that these derivatives are of diagnostic value in those patients who react poorly, or not at all, to one or the other or both types of ordinary tuberculin. In view of the fact that the derivatives, especially the *Ether-insoluble X* substance, contain but a very small part of the original tuberculin, these findings lend further support to the idea that the active principle of the tuberculin and by the same token, of the tubercle bacillus, is contained in some such derivative of tuberculin. The nature of this substance and a discussion of the chemical studies of the derivatives are the subject of another paper (6).

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A CASE OF CHRONIC TUBERCULOUS MENINGITIS SIMULATING BRAIN TUMOR[1]

LESTER R. WHITAKER[2]

The case here reported is one of generalized miliary tuberculosis, with meningitis, which ran a prolonged course and gave rise to the syndrome of an acoustic tumor in the left cerebello-pontine angle. No tubercle bacilli were found in the spinal fluid, nor were guinea pigs successfully inoculated, but such typical tubercles were present in the various organs at necropsy as to leave no doubt with regard to the diagnosis.

The patient, a married Canadian woman of 39 (*P. B. B. H., Surg. No. 22122*) was admitted to the hospital February 2, 1924, complaining of headache and disturbance of vision. Her *past history* was not important except for the fact that she had lost 19 pounds in weight during the last year. For some years also there had been progressive deafness with tinnitus in the left ear. The *present illness* began ten weeks before admission, when she awoke one morning with a severe suboccipital headache, and feeling dizzy, nauseated and weak. She vomited several times that day and at intervals during the following week. The headache continued. After five days in bed she got up, but complained of vertigo, and had a staggering gait. Eight weeks before admission she began to have double vision upon looking to the right, and soon noticed some loss of visual acuity. Moreover, her husband offered the information that she had had transient periods of irrationality for two months.

The *physical examination* showed a small but seemingly well-nourished woman, intelligent, coöperative, and able to be up and about the room. Her general examination was negative, though the right lung appeared slightly more dull to percussion than the left. No râles were heard. *Neurological examination* revealed bilateral choked discs of 3½ D., with much scar-tissue and a few small hemorrhages, visual acuity 20/30 with normal fields, a definite right abducens palsy, and no nystagmus. Hearing was normal in the right ear, but greatly diminished in the left; bone conduction was lateralized to the right; a caloric test gave no response on the left, but syringing the right ear evoked marked nystagmus to the opposite side with vertigo and vomiting.

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[2] Arthur Tracey Cabot Fellow, Harvard Medical School.

There was some dysmetria and incoördination with hypotonia of both upper and lower extremities, though her cerebellar signs in general were not pronounced. Reflexes were slightly exaggerated, and sensation was normal all over the body.

The *spinal fluid*, which had been examined before admission to the hospital, showed 40 lymphocytes per cu. mm.; globulin was not increased in it, and the Wassermann was weakly positive. This observation was not repeated in the hospital. The leucocyte count was 8,000. The blood Wassermann, reported in the hospital, was negative.

Briefly, then, the patient had headache, vomiting and dizziness of ten weeks' duration, with diplopia and blurring of vision; and showed choked discs 3½ D., deafness in the left ear and an inactive vestibular nerve on that side, some hypotonia, dysmetria and incoördination, and the loss of 19 pounds in one year.

Course in the hospital: For six days after admission the patient had a slight elevation of temperature, which twice reached 100°F. The choked discs increased to 4 D., and the vomiting persisted. The neurologist who referred the patient to the hospital, and those who subsequently examined her, were led to believe that she had a subtentorial tumor at the left cerebello-pontine angle.

A *cerebellar exploration* was performed six days after admission. Attempted punctures through the occipital region on both sides failed to reach either lateral ventricle, indicating at least the absence of an internal hydrocephalus. On exposing the cerebellum a definite dislocation of the left hemisphere toward the opposite side was found, giving the operator further reason to expect a tumor on the left. Exploration in the left cerebello-pontine angle revealed, however, no definite tumor. A small mass of suspicious looking tissue which protruded from the cerebellum in the recess was removed for microscopic examination. It showed typical miliary tubercles (fig. 1).

The patient had a stormy *postoperative course.* In spite of the fact that her choked discs soon subsided to 1½ D. on the right and 3 D. on the left and remained at about that level, her headaches persisted, vomiting was frequent, and she became irrational at times. She began to have attacks of abdominal distention with dyspnoea. Her temperature fluctuated, occasionally reaching 101° in the evening. The white count was 9,200. Three weeks after operation she had a gradual rise of temperature to 103.5°. The white count was then 16,000. Lumbar puncture revealed a clear, faintly yellow fluid under slight tension, which contained three lymphocytes per cu. mm., and an excess of globulin. Guinea pigs inoculated with 5 cc. of the fluid did not develop tuberculosis.

The patient then began to have considerable dyspnoea, and gave signs of fluid at the right base. Thoracentesis yielded a purulent material containing a varied flora, including streptococci. After the cavity was drained her condition temporarily improved, but she soon became more dyspnoeic, cyanotic, and finally unconscious. She died sixteen weeks after the onset of her illness and five weeks after the operation.

Necropsy findings: Externally, there was moderate general *lymph-node enlargement.* The mesenteric, lumbar and iliac, superior and inferior gastric lymph nodes were enlarged, moderately soft, opaque, gray, finely

FIG. 1. SECTION OF CEREBELLAR TISSUE REMOVED AT OPERATION SHOWING TWO GROUPS OF MILIARY TUBERCLES (OUTLINED BY ARROWS) × 60

granular and homogeneous. Both superior and inferior groups of mediastinal lymph nodes were enlarged, but moderately firm, one of them being calcified. None of the nodes showed caseation in gross.

The right *pleural cavity* was obliterated by adhesions, except for a small cavity containing 30 cc. of thick pus, a smear of which showed gram-positive cocci in pairs and short chains, and slender gram-positive rods with rounded ends. None of these bacteria would grow on any of the enriched culture media. Both *lungs* showed *miliary tubercles* throughout, with small areas of bronchopneumonia in the right lung.

The *brain* showed nothing unusual on the surface. There were several small hemorrhages in the white matter, in the region of the basal ganglia on both sides. The largest of these was located near the thalamus on the left side. It measured about 0.5 cm. in diameter and extended anteroposteriorly for a distance of about 3 cm. (Cf. drawing, fig. 2).

Microscopic examination of the tissues showed *miliary tubercles* throughout both *lungs*, in the *spleen*, and in the *liver*. One of the lung sections presented a small blood-vessel, in the wall of which was a tubercle filling nearly half of the

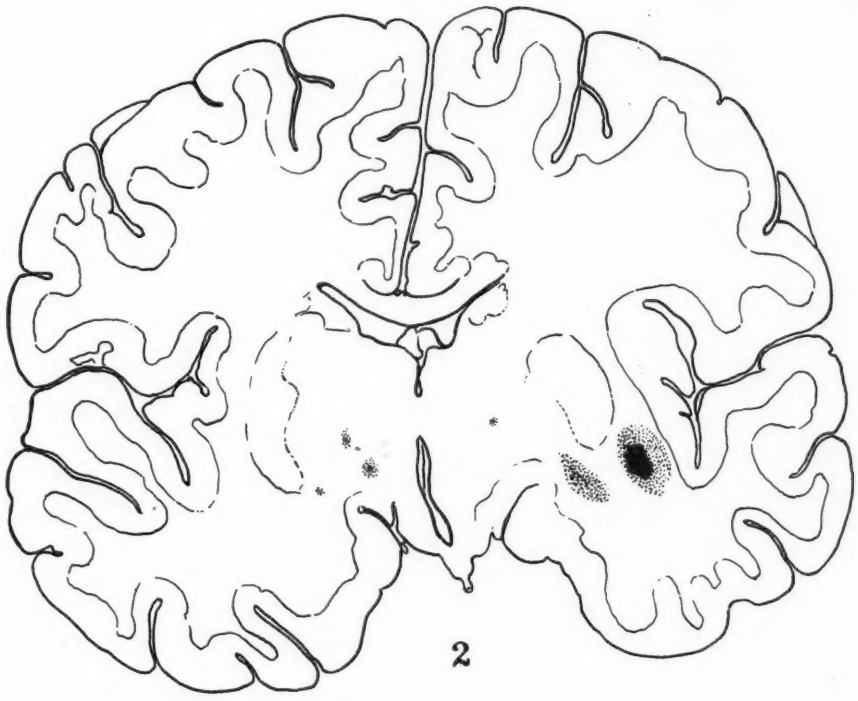
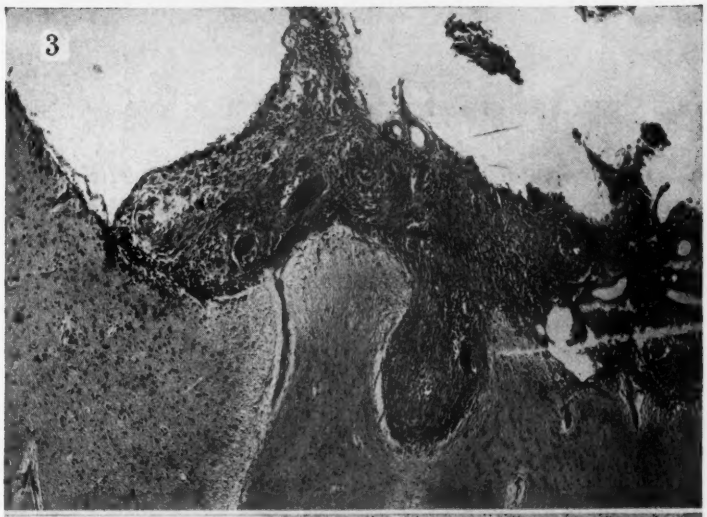
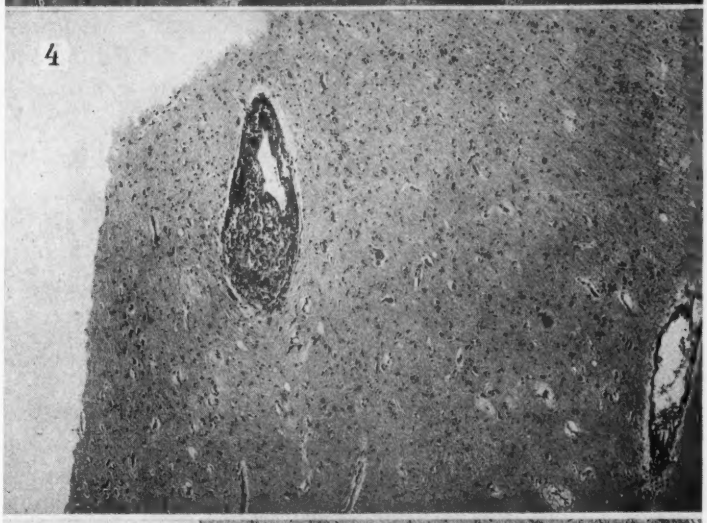


FIG. 2. DRAWING OF A CROSS-SECTION OF THE BRAIN SHOWING SEVERAL SMALL HEMORRHAGES INTO THE WHITE MATTER ABOUT THE BASAL GANGLIA

lumen. The sections of lymph nodes from the peritoneal cavity were packed with tubercles, showing giant cells and a good deal of structureless pink-staining material (caseation). These were the oldest lesions found.

The *meninges of the brain and cord* showed, in some places, an infiltration of mononuclear leucocytes, and typical miliary tubercles, sometimes in groups of four to six and having one or more giant cells (fig. 3). Occasional clumps of mononuclear leucocytes were found deep in the brain substance, especially in the vicinity of the small hemorrhages previously mentioned.





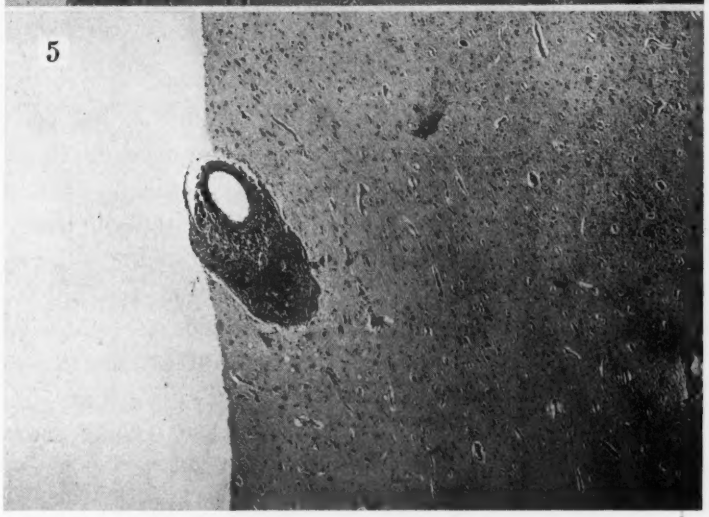


FIG. 3. TUBERCULOUS REACTION OF THE CEREBRAL MENINGES × 50
Note the marked fibrosis

FIG. 4. TUBERCLE IN THE WALL OF A CEREBRAL VEIN WITH PERIVASCULAR LYMPHOCYTIC INFILTRATION × 50

FIG. 5. A CEREBRAL ARTERY WITH PERIVASCULAR TUBERCLES × 50

Upon the suggestion of Dr. Wolbach that these hemorrhages into the brain substance may have been caused by tuberculous erosion of the vessel-walls, a search was made to find evidence of this process. Several perivascular tubercles were found, some of them actually invading the walls of the vessels (figs. 4 and 5), and one tubercle was found between the walls of an adjacent artery and vein. This would seem to be good evidence that these small cerebral hemorrhages were produced by tuberculous destruction of vessel-walls. The only mention known to the writer, of small hemorrhages into the brain substance in tuberculous meningitis was made by VanIngen (1) in a discussion of the pathology of this disease. Although microscopic examination in the case in question showed any number of typical tubercles in various tissues, an extensive search of specially stained sections failed to reveal the presence of tubercle bacilli. Likewise, guinea pigs inoculated intraperitoneally with spinal fluid proved to be negative for tuberculosis, though tubercles were found in the meninges and brain-substance of the patient after death. Necropsy, however, disclosed nothing to account for the patient's supposed acoustic tumor syndrome.

Note on the significance of the pathological findings by Dr. S. B. Wolbach: In spite of the widespread distribution of tubercles in this case, the histological evidence points toward a slow progress of the infection. Tubercles in the various organs, including the meninges, show an unusual degree of fibrosis. The conglomerate tubercles in the liver occasionally show caseation, while the miliary tubercles in the abdominal lymph nodes also show caseation. On the other hand one abdominal lymph node is almost completely fibrosed. The tubercles in the lungs seem to have undergone fibrosis almost as rapidly as they were formed. Because of this fibrosis and because of the tuberculous abdominal lymph nodes, a bovine source of infection is suggested by way of the alimentary tract.

DISCUSSION

Tuberculous meningitis is usually a part of a more or less generalized tuberculosis. It is less common in adults than in children; in adults its course is usually less severe and may become chronic.

The typical case in a child is rapid, terminating fatally in three or four weeks. There are, at first, signs of meningeal irritation, such as headache, irritability or irrationality, nausea, vomiting, photophobia, and stiffness of the neck and legs with exaggerated reflexes. Closely following these, and sometimes more or less concomitant, are signs of increased intracranial pressure,—more severe headache, drowsiness or coma, choked discs, ocular and other palsies, slow pulse, sighing and shallow respirations.

In adults the process is likely to be slowly progressive and occasionally localized (this is the fibrotic variety), with the result that symptoms of focal brain lesions and of increased intracranial pressure may come on gradually without the acute symptoms of meningeal irritation.

For example, Libby (2) believes that ocular disturbances, along with severe headache, are common enough manifestations of localized tuberculous meningitis in adults to be important in diagnosis. He says that tuberculous meningitis should be suspected when a patient with a previous history of tuberculosis has a sudden severe headache with disturbances of the eye, most commonly an abducent paralysis, ptosis of the lid, and pupillary disturbances or impairment of vision. He cites two cases, as follows:

A man with tuberculosis arrested for many years was attacked by a severe persistent headache, with unilateral ptosis, divergent squint and mydriasis. The optic discs and fundi were negative. After several days the patient developed a typical tuberculous meningitis. In the other case, a man with arrested pulmonary tuberculosis had a sudden impairment of vision with severe constant headache, and showed moderate optic neuritis. The differential diagnosis lay between brain tumor and syphilitic optic neuritis or tuberculous optic neuritis. Two weeks later the patient became totally blind and died of tuberculous meningitis.

Tuberculous meningitis with symptoms of a focal lesion and increased intracranial pressure has more than once been confused in diagnosis with brain tumor, as may be inferred from the following statements:

Landis (3) says,

A chronic form of the disease is not uncommonly seen in which there is a single tuberculous nodule which usually results from coalescence of several tubercles. This type of disease is often latent or may give rise to symptoms similar to those produced by brain tumor.

Bramwell (4), in discussing the differential diagnosis between brain tumor and tuberculous meningitis, has this to say:

Tuberculous meningitis may develop insidiously. Headache and vomiting, accompanied perhaps by focal brain symptoms, are often noted at an early stage. These phenomena may suggest the presence of an intracranial tumor; sometimes a local tuberculoma is actually responsible for symptoms which have failed to attract notice until a developing meningeal infection draws attention to its presence. Cases of this kind are sometimes submitted to operation at a time when there is no indication of involvement of the meninges. The writer can recall two such cases in which he advised operative intervention. A preceding period of ill health and loss of weight, and the somewhat rapid development of the clinical signs, may

be suggestive, while sooner or later some febrile disturbance, neck rigidity, Kernig's sign, and, it may be, a bilateral extensor response,—in other words, phenomena indicative of meningeal irritation,—make their appearance.

A few cases have been reported in which localized chronic tuberculous meningitis has produced syndromes of other localized processes.

Legry (5) reports the following case:

The patient, a woman of thirty-one, had suffered from lassitude for two months; and, for a week, tingling at intervals in the left hand and foot, extending to the left half of the body. The left knee jerk was exaggerated and the Babinski was positive on the left, with diminished sensation and motor power on that side. There was no vomiting, neck rigidity or Kernig's sign. Ten days later the temperature went to 39°C., and paresis came on in the right leg. Tubercle bacilli were found in the spinal fluid. After four days the meningitic syndrome became complete, and in four days the patient died. Necropsy showed, at the upper border of the right cerebral hemisphere, a thick granulomatous area slightly smaller than a silver half-dollar. There were only a few small grayish patches elsewhere in the meninges.

We have good evidence that this chronic form of tuberculous meningitis is curable in certain cases. Brooks and Gibson (6) report the case of a girl four years old, with a positive spinal fluid, who apparently recovered from tuberculous meningitis, though she died of bronchopneumonia six months later. Necropsy showed a slight general thickening of the meninges with small, whitish, flat elevations 1 mm. in diameter. This case indicates that even in a child tuberculous meningitis can be a mild slow process.

Cramer and Bickel (7) have studied the case of a boy of nineteen who was rather suddenly attacked by lassitude, headache, and pain in the neck, abdominal pain and diarrhea, vertigo and tinnitus. Upon physical examination he was unresponsive, and showed photophobia, sluggish pupils, stiffness of the neck and legs, a positive Kernig's sign, and slightly exaggerated reflexes. There was evidence of some consolidation at the right apex. Lumbar punctures at two different times showed a clear fluid under normal tension, with 82 and 280 cells per cu. mm., 72 and 60 per cent lymphocytes, respectively. Only a single acid-fast bacillus was found in smears, but injection of the fluid into a guinea pig produced tubercles. The blood Wassermann and spinal-fluid Wassermann were negative. The patient gradually improved until he left the hospital, nine weeks after the onset of his illness. He was seen, eighteen months later, in perfect health.

In this article Cramer and Bickel also report from the literature (up to 1922) 45 other cases of apparent cure of tuberculous meningitis, in which the diagnosis was proved by guinea-pig inoculation and the finding of tubercle bacilli in the spinal fluid. Two and a half per cent of the cases were under two and a half years and 30 per cent were over twenty years of age, indicating a large proportion of adults. Seven of the patients died of a relapse after two months to a year or longer. The remainder were in good condition from six months to three years later. Necropsy upon one of the patients who died of a relapse after four months showed plaques of old meningitic sclerosis with recent miliary eruption. One dying of pulmonary tuberculosis eight years afterward showed thickening of the meninges about the Sylvian fissures. Another, dying after several years, showed sclerosis of the meninges.

SUMMARY AND CONCLUSIONS

1. The case here reported is one of tuberculous meningitis running a mild course of sixteen weeks' duration, with symptoms very closely resembling tumor at the left cerebello-pontine angle.

2. At operation a small mass of tissue removed from the cerebellum at the left cerebello-pontine angle showed miliary tubercles of recent origin.

3. Necropsy revealed nothing to account for the supposed acoustic tumor syndrome, but showed a generalized miliary tuberculosis, with small sclerosed tubercles scattered throughout the pia mater and brain substance; and several small hemorrhages in the white matter at the base of the brain, the origin of which is unexplained, but which, judging from the perivascular location of many tubercles, may have been due to erosion through vessel walls.

4. This case represents the slowly progressive fibrotic type of tuberculosis, which may be limited in extent and give symptoms resembling other localized processes, and which may occasionally undergo spontaneous healing.

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TUBERCULOUS MENINGITIS IN CHILDREN

A STATISTICAL STUDY OF THE DISEASE FROM BIRTH TO FIFTEEN YEARS OF AGE[1]

BEATRICE SLAYTON HERBEN AND M. ALICE ASSERSON

Although tuberculous meningitis has probably been the most fatal form of tuberculosis, it was not until 1768 that the scientific world acquired a true and complete picture of the disease. It has undoubtedly been recognized since Hippocrates, who gave descriptions of inflammation of the central nervous system in which there were included accounts of what we know as meningitis of tuberculous origin; and, while he makes no distinction between the disease in adults and that in children, he was the first to note that age has an important influence, for he found it "very common in the newly born and up to the age of seven." It is an amazing fact that Stoll, in the latter part of the eighteenth century, caused a widespread acceptance of Galen's theory (1) that the principal cause of this malady was the bile. It is also of particular interest to pediatricians that in the tenth century, when the first treatise on diseases of children appeared among Arabian authors, Rhazes, entitling his third chapter, *De Magnitudine Capitis Puerorum*, considered only chronic hydrocephalus without any reference to meningitis. Cumston (2) credits Sauvauges with being the first to give, in 1788, a short and accurate description of the disease, but it is with Robert Whytt (3) that the distinction rests of publishing, also in 1768, an almost complete description of tuberculous meningitis, and it was owing to this classic treatise that the profession completely changed its attitude toward this infection, and from the date of its publication there have been accumulating such facts as are now held in the modern conception of tuberculous meningitis.

In this country, in 1833, Gerhard (4) of Philadelphia was the first to call attention to this disease; but, in spite of this long record of observation, at the present time there are unsolved problems and phases of the subject which remain obscure. When we consider that approximately 4,500 children, under 15 years of age, annually die from tuberculous

[1] Made under the direction of the Children's Committee of the New York Tuberculosis Association.

meningitis in the entire United States, it would seem imperative that we acquire definite knowledge of every factor involved in the maintenance of this fatal form of tuberculosis. For example, while Koplik (5), Pottenger (6), and others express the opinion that in the majority of cases of tuberculous meningitis, especially when occurring in young children, a history of contact with a patient suffering from active tuberculosis could be ascertained, in point of fact such a history does not seem to be given. One has only to go over hospital records to find an enormous number of cases in which it is stated "no history of contact obtained." One question arising therefore concerns the mode of infection. If it be not human contact, what part is played by milk infection? Just what has housing to do with this form of tuberculosis? Is there a racial susceptibility involved in this aspect of the infection, and how does season influence racial susceptibilities?

It was with these and other questions in mind that there was undertaken by the Children's Committee of the New York Tuberculosis Association a comprehensive review of the subject and a thorough study of a number of cases of tuberculous meningitis occurring in New York City. Through the courtesy of Dr. Louis I. Harris of the Health Department, Dr. William H. Park and Dr. Josephine B. Neal of the City Research Laboratories, and with the coöperation of several hospitals, we were enabled to study 135 cases of tuberculous meningitis in children, from birth to fifteen years of age; visiting the homes of the immediate families and of the relatives and neighbors, as well as investigating 210 tenement houses, with a view of ascertaining the relation between any tuberculosis found therein and the cases of tuberculous meningitis under attention. The Health Department gave us access also to the death records of 435 cases of tuberculous meningitis in children throughout the Borough of Manhattan.

MODE OF INFECTION

There is some difference of opinion as to the mode of infection. Pirquet, basing his conclusions upon a study of 1,060 autopsies, stated that the human bacillus entering the lungs is the cause of tuberculosis in children, and Jeanneret (7) was so impressed with the danger of tuberculous meningitis in infants of tuberculous parentage that he advocated removal of the child from its parents immediately after birth. On the other hand, Meyer (8) reported 105 cases of tuberculosis in children of which 73 per cent gave no history of contact, and his findings are similar

to those of others, such as H. Koch (9), who in the study of 75 cases found only 23 per cent having tuberculous parents. Abt (10) probably made a correct observation when he claimed that tuberculosis is not acquired in a single way, the mode of infection differing in the different localities.

In New York City, in our series of 135 cases, the hospitals and private physicians reported a history of contact obtained in 19 per cent and no history of contact in 81 per cent. By careful investigation we obtained in these same cases a definite history of contact in 56 per cent, a history of probable contact in 18 per cent, a suspicious history of contact in 10 per cent, and no history of contact in but 16 per cent of these cases. Of 30 cases, 12 gave a definite history of contact with a tuberculous mother, the father was the source of infection in 9 other cases, and the remaining 9 cases were in contact with active tuberculosis in uncles or aunts.

The theory of milk infection seems to be untenable in these cases. Only 33 of the 135 cases had been given loose milk (milk supposedly pasteurized but unbottled), and of these 33 children, 16 or 49 per cent gave a definite history of contact with active tuberculosis, 11 or 33 per cent gave a history of probable contact, 3 or 9 per cent gave a suspicious history, and only 3 cases or 9 per cent gave no history of contact.

Koch bears testimony to the fact that breast-fed infants are not protected from tuberculous meningitis. He found among infants, from birth to three years of age, that 82 per cent of such cases were breast-fed and 18 per cent artificially fed. Abt states that 86 per cent of all cases of tuberculous meningitis occur in breast-fed children. The question of breast milk containing tubercle bacilli would seem to be of minor importance, for various observers have examined the milk of tuberculous women and have not demonstrated the presence of tubercle bacilli, except in such few cases as had mammary involvement; and it is of interest to note in this connection that Hess (11) found that in 18 children who drank milk in which tubercle bacilli were present all but one had remained free from tuberculosis for a period of three years (that is, to date of his report).

Bovine infection through milk has occupied attention since Villemin, in 1865, infected animals with tuberculous material and noted the difference in the virulence of material from human and bovine sources. Park and Krumwiede (12) concluded from a study of 1000 cases that "on the whole, bovine infection causes somewhat less than 10 per cent of the total deaths from tuberculosis in children." Park and Williams (13)

assert that the meninges are less commonly infected by the bovine than the human bacillus. Even in bovine infection human contact as the source cannot be ruled out entirely. Allan has recorded an interesting case of an infant dying of tuberculous meningitis, which was caused by the bovine bacillus, and believed to have been acquired from another child in the family who suffered from tuberculosis of the cervical lymph nodes with an associated oral focus.

When there is added to this evidence the findings of Miller and Woodruff (14), who discovered 51 per cent of 150 children with tuberculous parents infected with tuberculosis, and the report on 135 tuberculous children by Moorman (15), who found only 15 cases giving no history of contact, it scarcely seems necessary to emphasize the importance of human contact, but the following remarkable series of cases is worthy of quotation:

In 1878 Dr. Hubert Reich (16), District Physician of Mühlheim, reported that he saw 10 infants of healthy families die of tuberculous meningitis within fourteen months. "These cases occurred in the practice of a midwife who had severe tuberculosis, and was accustomed to inspire air from mouth to mouth in cases of asphyxia and to kiss upon the mouth all children at whose birth she assisted. One child died at two and one-half months of age, 7 died between 3 and 4 months, one at 6 months, and one at 9 months."

Therefore, from a study of the literature and of our series of 135 cases it would seem necessary to conclude that, while in localities where milk is not pasteurized, bovine infection may play a part in the prevalence of tuberculous meningitis, in New York City where 98 per cent of the milk supply is pasteurized it is a negligible factor. We believe that infection acquired through contact with active tuberculosis in human beings is the chief cause of tuberculous meningitis in children in this city. In the light of the fact that by careful study in each of the 135 cases we obtained the definite history of contact in over half the cases and that in only 13 was there no suspicious history of contact, we suspect that were it possible to obtain complete evidence in every case of tuberculous meningitis the great majority of cases would show human contact as the source of infection.

TENEMENT HOUSES AS AN ETIOLOGICAL FACTOR

When it is considered that tuberculous meningitis is most prevalent in the congested districts of this city, where children are forced to live in

crowded tenement houses and are taken for air and recreation to the crowded streets, the possibilities for tuberculous infection are seen to increase to the point where it is not reasonable to call any child of these families a noncontact case. In the course of our study we endeavored to obtain information regarding the actual relationship existing between such possibilities for infection and the case itself. In connection with 135 cases of tuberculous meningitis more than 281 tenement houses were investigated from this point of view. Personal visits were made, and every case obtained was afterward submitted for verification, through the registration files of the Health Department, the death records and to the private physicians, and only such cases as could be proved to be tuberculous are recorded in tables 1, 2 and 3. Data were obtained from the registration files of the Board of Health, City of New York, for 281 houses. The number of houses with no tuberculous cases on file was 71, and the number of cases of tuberculous meningitis associated with active tuberculosis in the apartment occupied by the patient was 29.

In one of the 4 cases of table 1 there was no history of contact with tuberculosis in the family, friends or neighbors, the family having come into its apartment immediately after the removal of the previous occupant, who had active tuberculosis and there was no disinfection of the premises. Is it of significance that the child who was born one year and nine months later, and who was in perfect health, developed tuberculous meningitis at the age of one year and three months? It would be well to recall here Veiller's (17) warning that in the absence of radical measures for renovation and disinfection there is every reason to expect continued prevalence of tuberculosis among tenants of such houses as have sheltered tuberculous patients, no matter how frequently the occupants may change.

Holding in mind that no case of active tuberculosis was accepted as such, until it was proved by the registration files or by private physicians, it is impressive that, of 123 tenements, in 39 instances there was unquestionable contact with tuberculosis with other tenants in the building and not in the immediate families of the victim. A brother and a sister, aged 2 and 3 years, respectively, developed tuberculous meningitis within three months of each other, and the source of infection of these two children was a tuberculous adult who lived in another apartment on the same floor. In 15 cases, while it could not be absolutely proved that there had been contact with tuberculous patients in other apartments, it was considered highly probable. In 7 cases it was questionable that

there had been such contact; and in 9 cases, in which no history of contact could be obtained, there was nevertheless tuberculosis elsewhere in the tenement in which these tuberculous meningitis cases developed.

TABLE 1

Number of apartments having had a tuberculous occupant immediately preceding the residence of patient	4
Where patient showed positive history of contact	1
Where patient showed probable history of contact	0
Where patient showed suspicious history of contact	2
Where patient showed no history of contact	1

TABLE 2

Number of tenements showing tuberculous cases in other apartments at time of residence of tuberculous meningitis case	210
Where patient showed positive history of contact	123
Where patient showed probable history of contact	42
Where patient showed suspicious history of contact	17
Where patient showed no history of contact	28

Note: The frequency with which the domicile of this class of people is changed is well recognized. The above table emphasizes the fact that little children may be subjected not once but many times to contact with disease in several residences. For 135 cases of tuberculous meningitis, to check the number of possible contacts with active tuberculosis, it was necessary to visit 281 tenements which at some time had served as homes to these children, and it was found that 210 of these dwellings had housed patients with the actual disease.

TABLE 3

Number of cases showing no tuberculosis reported in same tenement	30
Cases showing positive history of contact	7
Cases showing probable history of contact	3
Cases showing suspicious history of contact	7
Cases showing no history of contact	13

Note: The cases showing positive, probable and suspicious histories of contact had that association with tuberculosis through nonresident relatives and friends.

The sanitation of individual apartments and of the houses in general was considered, and it was discovered that in 32 cases of tuberculous meningitis the sanitation throughout was very poor, in 43 it was only fair, and in the 56 other houses it was fairly good. Only two children were found in clean light homes which cannot be grouped with tenements.

Out of 56 cases living in houses classed as having fairly good sanitation, 33 showed positive history of contact, 12 probable, one questionable, and there were but 10 with no history.

DISEASES PRECEDING ONSET OF TUBERCULOSIS

Before leaving etiological considerations, attention should be called to the influence of previous diseases on the onset of tuberculous meningitis. Otitis media, measles, pneumonia and whooping cough seem to constitute an important factor. H. Koch (18), in 305 cases, found that 129 had had measles, 60 of these having occurred within a year preceding meningitis and 21 within the preceding four months. In 10 cases a direct relationship between measles and meningitis was proved. In 4 cases a direct relationship was established with whooping cough. Abt

TABLE 4

Cases showing previous diseases

	NUMBER	PER CENT
Number of cases	135	
Otitis media	18	22.8
Measles	17	21.5
Pneumonia	11	13.9
Whooping cough	8	11.4
Bronchitis	9	10.1
Tonsillectomy	7	8.9
Influenza	6	7.6
Chickenpox	3	3.8

considers the relationship between tuberculous meningitis and measles and whooping cough to be striking.

Another important concomitant of tuberculous meningitis Hutinel and Merklen (19) found to be congenital syphilis, causing a localization of tubercle bacilli in the meninges due, they considered, to decreased resistance of these parts. Carnot and Gardin (20) reported the case of a previously healthy girl who developed tuberculous meningitis two days after having been bitten by a mad dog and receiving antirabic vaccine. (This patient had lost a brother with tuberculous meningitis several years before, and was, therefore, considered to have had a latent tuberculous infection.)

Seventy-nine or 58.7 per cent of our 135 cases gave a history of previous diseases.

These conditions preceded tuberculous meningitis by not more than four months and most of them by less than three months. A few cases, which on autopsy showed a generalized tuberculosis, gave a history only of "digestive disturbances during teething." The cases preceded by tonsillectomy are notable in that there was no other disease preceding the onset of tuberculosis, and inasmuch as Mitchell (21) in Edinburgh (1917) claimed to have found 100 children and 6 adults with primary tuberculosis of the tonsils, associated with tuberculosis of the upper cervical lymph nodes, the finding of 7 cases preceded only by tonsillectomy is noteworthy. When children are in contact with active tuberculosis and, therefore, in all probability infected with tubercle bacilli, would it seem that acute infectious disease or tonsillectomy carry peculiarly dangerous possibilities? In the following table it can be seen that in a preponderance of cases of tuberculous meningitis a positive history of contact is coupled with the presence of a preceding disease.

TABLE 5

Correlation of history of contact with onset of tuberculous meningitis when preceded by disease

HISTORY OF TUBERCULOSIS CONTACT	POSITIVE	PROBABLE	SUSPICIOUS	NEGATIVE
Measles	12	1	3	1
Whooping cough	6	0	2	0
Pneumonia	8	2	0	1
Otitis media	9	1	5	3
Tonsillectomy	4	2	1	0
Influenza	4	1	0	1
Bronchitis	3	3	2	1
Chickenpox	2	1	0	0
Total	48	11	13	7

SEX AND AGE

Sex is not an influential factor in this disease. Koch found 145 boys and 157 girls in a series of 302 cases, and Meyer in 105 cases found 53 per cent females and 52 per cent males.

In 135 cases we found that 73 or 54 per cent were males, and 62 or 46 per cent were females. In a series of 435 cases studied from death certificates, 232 or 53.3 per cent were males, and 203 or 46.7 per cent females.

A very important aspect of tuberculous meningitis is its predilection

for infants and young children. Artamanoff (22) gives about 30 per cent of cases occurring under three years of age. The largest number of cases reported by Holt (23) in a series of 300 occurs between 9 and 12 months, and Meyer in 105 cases found 30 per cent occurring between 2 and 3 years of age. Koch found 68 per cent occurring before the end of the fourth year of life, with the largest absolute number of cases in the second year. In an observation of 15 cases occurring in over a year at

TABLE 6

AGE GROUPS	SERIES OF 135 CASES	
	Cases	Per cent
From birth to end of first year	20	14.8
From 1st to 2nd years of age	30	22.3
From 2nd to 3rd years of age	25	18.5
From 3rd to 4th years of age	13	9.6
From 4th to 5th years of age	12	8.9
From 5th to 10th years of age	20	14.8
From 10th to 15th years of age	13	9.6
Correct age unknown	2	1.5

TABLE 7

Age groups correlated with history of contact (series of 135 cases)

AGE	POSITIVE CONTACT		PROBABLE CONTACT		SUSPICIOUS CONTACT		NEGATIVE CONTACT	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
0–12 months	7	35.0	7	35.0	1	5.0	5	25.0
1– 2 years	19	63.0	2	6.7	3	10.0	6	20.0
2– 3 years	13	52.0	4	16.0	3	12.0	5	20.0
3– 4 years	9	69.2	1	7.7	1	7.7	2	15.4
4– 5 years	7	58.3	2	16.7	1	8.3	2	16.7
5–10 years	12	16.0	5	25.0	3	15.0	0	0
10–15 years	6	46.1	4	30.8	1	7.7	2	15.4

the Postgraduate Hospital, Alexander (24) found 50 per cent to be between 1 and 2 years of age.

Dr. Josephine Neal (25), in a series of 623 cases, found the age distribution to be as follows: Under 3 months, 5; 3 to 6 months, 19; 6 to 12 months, 74; 1 to 2 years, 167; 2 to 3 years, 79; 3 to 5 years, 9; 5 to 10 years, 93; 10 to 20 years, 52; over 20 years, 44. It will be noted here that she found that children from 1 to 2 years were the most susceptible.

The youngest in our series of 135 was four months and the greatest number of cases occurred between 1 and 2 years of age, the next highest being from 2 to 3 years of age.

In the series of 435 cases studied through death certificates the youngest was one month and twenty-five days old, and again the greatest number of cases occurred between the ages of one and two years (24.6 per cent); 75.7 per cent of all the cases occurred before the fourth year (328 cases); from 5 years to 10 years there were 78 cases or 17.9 per cent; and from 10 to 15 years of age 28 cases or 6.4 per cent.

TABLE 8

AGE GROUPS	SERIES OF 435 CASES	
	Cases	Per cent
Birth to one year	85	19.6
1st to 2nd year	107	24.6
2nd to 3rd year	70	16.1
3rd to 4th year	39	8.9
4th to 5th year	28	6.44
5th to 10th year	78	17.8
10th to 15th year	28	6.44

RACE

Eighty per cent of 135 cases of tuberculous meningitis belonged to American, Jewish, Italian, Irish and Negro stock.

TABLE 9

135 tuberculous meningitis cases according to race

	CASES	PER CENT
Italian (born in Italy or parents born in Italy)	35	25.8
American (parents born in America)	34	25.2
Jewish (both parents Jewish)	16	11.9
Irish (born in Ireland or parents born in Ireland)	16	11.9
Negro (one or both parents Negro)	7	5.2
Other races	27	20.0

In spite of the fact that the population of American-born children in New York City exceeds the number of children of Italian parentage the latter group furnished about an equal number of cases of tuberculous meningitis. It would seem therefore suggestive that the Italian baby may have a greater susceptibility to tuberculous meningitis. The Irish, Jewish and Negro stocks show a high susceptibility to this form of

disease as compared with other and mixed races. (It is most unfortunate that at the time of this writing the rates of population in this age group from birth to 15 years cannot be given.)

In our second series it is again the Italian who reveals the most striking susceptibility to tuberculous meningitis.

SEASON

Tuberculous meningitis in children occurs most frequently in the spring, and tuberculous meningitis in adults, in whom there is not the correlation between meningitis and measles and whooping cough, shows a

TABLE 10

435 cases of tuberculous meningitis according to race

	CASES	PER CENT
Italian	115	26.5
American	91	20.9
Jewish	84	19.3
Irish	41	9.4
Negro	37	8.5
Other races	67	15.4

TABLE 11

435 cases according to season

	CASES	PER CENT
December, January, February	88	20.2
March, April, May	160	36.8
June, July, August	104	23.9
September, October, November	83	19.1

rise in spring. Is there any value in the suggestion made by Albinger (26) that owing to these facts, and to the frequency of meningococcus infection at this season, there must be an increased susceptibility of the meninges to disease owing to the sudden changes of temperature and other weather conditions? Most authorities give March or April as the month that this disease reaches its peak, but Secker of Hamburg (27) finds in August and September the greatest number of cases, and Stelling of Kiel (28) gives April and November as "peak" months.

In the series of 435 cases 160 children, or about 37 per cent, succumbed to tuberculous meningitis in the spring months with the next highest incidence in the summer months.

While this generalization was maintained in the Italian, Irish and American races, in the Jewish and Negro races the highest peak was reached in midsummer, but the number of cases is so small that further observations on this point should be undertaken.

SPINAL FLUID

In tuberculous meningitis the spinal fluid is increased in amount and is clear or slightly hazy as a rule. Occasionally this haziness may be decidedly pronounced. Although it is not, as was formerly thought, pathognomonic of tuberculous meningitis, a fibrin web forms over the surface of the spinal fluid on standing. The cells are increased, and in a majority of cases the mononuclear cells are predominant. In rare instances in which there is a hazy fluid there may be an excess of polymorphonuclear cells.

TABLE 12

Racial susceptibility according to season in 435 cases

RACE	DECEMBER, JANUARY, FEBRUARY		MARCH, APRIL, MAY		JUNE, JULY, AUGUST		SEPTEMBER, OCTOBER, NOVEMBER	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Italian	22	19.1	47	40.9	30	26.1	16	13.9
Jewish	13	15.5	26	30.9	27	32.2	18	21.4
American	22	24.2	33	36.1	19	20.9	17	18.7
Irish	10	24.4	12	29.3	9	21.9	10	24.4
Negro	7	18.9	10	27.1	12	32.4	8	21.6
Other races	14	20.9	32	47.8	7	10.4	14	20.9

Albumin and globulin are always increased but the amount of increase varies considerably in different cases. Early in the disease the sugar content of the spinal fluid may be normal or almost so, but this condition lasts but a short time and, as the case advances, diminishes, and by qualitative methods of determination may become apparently absent.

Culturing and typing of spinal fluids were done for us under the direction of Dr. Josephine B. Neal, who stated that with expert workers tubercle bacilli should be demonstrated in from 70 to 75 per cent of the cases. Owing to various handicaps we obtained tubercle bacilli in only 47 specimens. Closely parallel to a series of fluids studied by Novick (29), in 3 of which the bacilli were found to be bovine in type, our series of 47 specimens were found to contain bacilli of human type

except in 3 instances which were bovine (6 per cent). In a recent report made by Gordon and Brown (30) in Boston, in 3 out of 19 cases of tuberculous meningitis the bovine type of bacillus was found (15 per cent).

AUTOPSY FINDINGS

During the course of investigation of 135 cases, 12 autopsies were obtained, and of this number 10 showed generalized miliary tuberculosis with tuberculous meningitis, while 2 cases were found to have a localized lesion with meningitis, and one case showed tuberculous meningitis only. This last-named case was of a child fifteen years of age. All the patients showing generalized miliary tuberculosis were three or under three years of age, except one who was five years old. Of the 2 cases evidencing a localized lesion one was two and the other ten years of age. These findings, in a small way, corroborated the observation made by Wollstein and Bartlett (31) "that the younger the patient the more general is the tuberculous infection."

It is the consensus of authoritative opinion that the lungs and the bronchial lymph nodes are the seat of the primary lesion in tuberculous meningitis. Pirquet (32) found that of 1,060 autopsies only 7 cases showed a primary intestinal lesion, and upon this study he bases his conclusion that tuberculosis in children is caused by the human bacilli entering the lungs.

In the postmortem examinations of Wollstein and Bartlett no healed lesions were found, but McCarthy (Phipps Institute Reports) has found from time to time evidence of healed lesions in the central nervous system.

DIAGNOSIS AND SYMPTOMS

There is nothing in our study which warrants adding to the already extensive literature on the questions of diagnosis, differential diagnosis and symptoms. (A detailed exposition of these subjects can be found in *Meningitis Tuberculosa,* H. Koch, *Ztschr. f. Kinderhk.*, 1913, vi, 263–373.)

DURATION

The duration of illness in our series of 135 cases was found to average 18 days.

PROGNOSIS

Ninety years after Whytt's paper, Rilliet wrote of healing tuberculous meningitis, but more than thirty years prior to his report Charpentier in 1829 published an amazing work, based on facts collected at the Children's Hospital in Paris, in which he made the astonishing claim of cures in nearly all of his cases. However, Harbitz (35) gives 40 as the total number of cured cases, up to 1921, in which the diagnosis was proved to be tuberculous meningitis. As the cases which recovered were among older children and adults, he considers that the increased resistance, due to the age of the patients and also to the benign forms of the disease, were important factors in their recovery. In general it is held that the disease in children is fatal and therapy of no ultimate value. In the series of 135 cases in children under 15 years of age presented in this study there was no recovery, and the fact that the data from 435 cases was derived from death certificates speaks for itself.

CONCLUSIONS

1. That in almost all of the cases of tuberculous meningitis in children of New York City the cause of the disease is the human type of tubercle bacillus derived through the child's contact with persons suffering from active tuberculosis. This form of infection is most prevalent in the least sanitary and most congested districts, and tenement houses present a most formidable aspect among etiological factors.

2. The evidence is predominantly against milk infection as a cause of tuberculous meningitis in New York City.

3. Otitis media and acute infectious diseases, especially measles, pneumonia and whooping cough in children in contact with active tuberculosis, carry a peculiar menace. The fact that about 9 per cent of our cases were preceded by tonsillectomy, unassociated with any other disease, would lead to the suggestion that further research be done along this line.

4. Sex is not an important factor, males being only slightly in preponderance.

5. The highest mortality from tuberculous meningitis occurred in young children, the greatest number of cases in a single age period developing in children from 1 to 2 years of age.

6. In terms of absolute numbers only, outside of the American stock, there was more tuberculous meningitis among the Italians than in other racial groups.

7. While this study verifies the accepted view of the great prevalence of tuberculous meningitis in the spring, this disease among the Jewish and Negro races reached its peak in midsummer.

8. In 47 specimens of spinal fluid showing tubercle bacilli, the latter were bovine in type in only 3 instances.

9. At autopsy 10 of 13 cases showed generalized miliary tuberculosis, 9 of which were under 3 years of age.

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EXPERIMENTAL TUBERCULOUS MENINGITIS[1]

SUPERINFECTION OF THE MENINGES IN RABBITS

WILLARD B. SOPER AND MORRIS DWORSKI

As the importance of superinfection in the pathology of tuberculosis is more and more appreciated, work is continually being done to throw new light upon its mechanism; for a comprehension of the phenomena of superinfection is indispensable not only for the understanding of tuberculous disease but also in the search for its cure. The article by Baldwin and Gardner (1) served to summarize the work on this subject up to 1921.

In this paper of ours we have deliberately adopted the term *superinfection* instead of *reinfection*. We agree with the French that the term *immunity of superinfection* implies a dependence upon another infection which is not only prior in time but also still existing, whereas the term *immunity of reinfection* does not imply all of this and should be reserved for the form of immunity observed after the acute infectious diseases, such as smallpox, measles, diphtheria, typhoid fever, etc.

As is well known, the so called Koch phenomenon is the basis of superinfection studies in tuberculosis, and the phenomena of superinfection have been demonstrated to declare themselves not only in the skin but also in the peritoneum, lungs, pleura, kidney and liver of various experimental animals. The mechanism of the phenomenon is still incompletely understood, although it is fairly generally accepted that one of its elements is a bacteriolysis whereby the superinfecting bacilli are quickly destroyed, either at the point of inoculation or at the point of their arrest. Also, it has been demonstrated that if the superinfecting dose into the sensitized animal exceeds a certain quantity the animal may die of shock, or may be overwhelmed and succumb earlier than the control animal infected for the first time; on the other hand, if the superinfecting dose be sufficiently small in amount it may excite no more than an imperceptible reaction and leave no trace behind.

On the basis of work previously done in this laboratory and of superinfection studies in general there seemed no good reason why the meninges

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should respond to superinfection by the tubercle bacillus in a manner different from the pleura and peritoneum. We were convinced of the possibility of demonstrating, experimentally at least, that tuberculous meningitis can heal itself and leave the animal little or none the worse for its presence.

We have sought to throw more light on several phases of this involved phenomenon, such as the effect of the size of the superinfecting dose, the difference in the more or less immediate response to the superinfecting dose in the allergic animal as compared with the normal control, the behavior of the cells in the cerebrospinal fluid during the progression or the recession of the meningitis; the question as to whether the animal may survive, and, if so, what evidence is left behind of its formerly active disease.

Although there have been a number of researches into experimental tuberculous meningitis they have all been with a view of studying pathogenesis, pathology or methods of treatment. In these, bacilli were introduced either by injection into the carotid artery, by trephining, or through a needle inserted into the lumbar spine, all of them unsatisfactory methods. We can find nothing in the literature on experimental superinfection of the meninges, although Calmette in his recent book alludes to its desirability. We must acknowledge our indebtedness for his suggestion.

TECHNIQUE

The rabbit was chosen as a much easier subject than the guinea pig for inoculation of the meninges and withdrawal of cerebrospinal fluid. We began by infecting our animals by the postorbital route, but this portal of entry was abandoned on account of the uncertainty of the needle point being always where desired, and of the impossibility of subsequently obtaining fluid for examination. Another means had to be found, and we hit upon that of puncture of the occipito-atlantoid ligament, to find a little later that Wegeforth, Ayer and Essick (2) had used this method and described it at length in 1919. We would add only one point to their excellent description and that is to accentuate the desirability of complete anesthesia of the animal. Without it there is often a reflex contraction of the neck muscles, which makes it difficult at times to orientate oneself. Also we attach a 1 cc. tuberculin syringe to our needle and quickly withdraw the necessary amount of fluid. The method is very satisfactory and, while one is not always successful, it is, nevertheless, fairly easy to

obtain 0.1 to 0.3 cc. of cerebrospinal fluid from the rabbit, as well as to infect the meninges. As demonstrated in the above-mentioned article, the needle point should lie in the *cisterna magna*, and any infecting solution introduced therein quickly bathes the whole subarachnoid space.

To render our animals allergic we used strains of human bacilli; in some series, H37, and in others, H60, both of them Saranac Laboratory strains and relatively avirulent for the rabbit. From 3 to 4 mgm. of an emulsion of one or the other of these bacilli grown on broth were injected subcutaneously into the right groin of each animal. After three to four weeks the lot of animals was tested intracutaneously with 0.1 cc. of 10 per cent Old Tuberculin. All gave some sort of positive reaction and most of them a good reaction. The same number of normal animals, as similar as possible in sex and size, was used as controls. Both lots were inoculated intrameningeally at the same time with bovine tubercle bacilli, control and allergic animals being done alternately. The bovine bacillus used was the B1, originally isolated in the Saranac Laboratory and of known virulence for the rabbit. The emulsion was always prepared from a weighed quantity of bacilli grown on glycerine-broth, and dried between sterile blotting papers. The bacilli were first triturated with a couple of drops of sterile ox-bile, after which normal saline solution was added in the proper amount and the emulsion further triturated. The final dilution was always such that the inoculation quantity, 0.1 cc., contained the desired amount of bovine bacilli. The emulsion never failed to show a certain number of clumps on slides made from it, but in this experiment it was deemed wiser to know the quantity of bacilli than to sacrifice this knowledge by centrifugating the clumps away.

No very great difficulty was experienced in drawing off cerebrospinal fluid from time to time, so that a study of cells at various intervals after meningeal infection was possible. All spinal-fluid cell counts were made immediately upon withdrawal of the fluid. Two pipettes were used, one for the total number of all cells, diluting with Hayem's solution; the other for white cells, using acetic acid. The difference between these counts gave the red-cell count. Wright's stain was used for differentials. The examiner never knew, until his results were tabulated, the number of the rabbit whose cells he was counting.

The animals were allowed to die in most cases, or perhaps killed if moribund. Complete autopsies were always done, with the exception of the spinal cord which was not removed, the brain being cut away a

little below the medulla oblongata. The brain and a section of lung were always hardened in Zenker's solution with 5 per cent formol or glacial acetic acid. Other organs were hardened when there was any suggestion of their involvement.

Control and superinfected animals were always inoculated alternately and the fluids removed alternately. Needless to say, the two sets of rabbits were kept under the same conditions as to air, sunlight, feeding and general care.

CLINICAL COURSE AND WEIGHTS

During the first four or five days after the intrameningeal injection there was nothing to be noted in the control animals. The superinfected animals, on the other hand, seemed to be ailing, although not ill. They continued to eat but were less lively. Then, after a few days, all of the animals appeared none the worse for their meningitis. But before long, depending on the dosage, the controls began to show symptoms, usually an inclination to remain still, or a little weakness in the hindquarters,or a tremor. Soon the hair became rough, the animal grew perceptibly thinner, weakness in the hindquarters progressed, complete paralysis behind and incontinence of urine and feces ensued. Paralysis of the forequarters was a late development, at least to any striking degree. Finally, there were retraction of the neck, complete loss of appetite and inability to move. This description applies equally well to the superinfected animals progressing to death. We have never seen an animal survive, once it showed any definite paralysis. As a rule, the superinfected animals survived the appearance of palsy longer than did the controls.

The weight curves were quite characteristic. The control animals, without exception, showed an almost uninterrupted fall in weight. One of these weight series will serve practically for all of the controls: *Rabbit 114, injected intrameningeally February 28:* Weight, February 29, 2381 gm.; March 13, 2324 gm.; March 20, 2154 gm.; March 27, 2013 gm.; April 2, 1928 gm.; April 8, 1956 gm.; April 24, 1532 gm. Death occurred on April 27th. Slight weakness was first noted on April 2nd.

The weights of the superinfected rabbits on the other hand, after falling to a lesser extent during the first two to four weeks after infection of the meninges, then again ascend to the normal figure, and remain there unless the course of the meningitis becomes progressive. In fact, the weight curve of the superinfected animal afforded usually a very good index as

to whether the rabbit was to survive or die. If the weight suddenly began to fall after having been maintained for some time, this fall was the forerunner of symptoms of meningitis and of death. The weights of such an animal are given: Rabbit 111, injected intrameningeally February 28: Weight March 1, 2097 gm.; March 13, 1899 gm.; March 20, 2182 gm.; March 27, 2126 gm.; April 2, 2098 gm.; April 8, 2211 gm.; April 16, 2182 gm.; April 24, 1814 gm.; May 2, 1815 gm.; May 12, 1814 gm.; May 19, 1587 gm.; May 27, 1531 gm.; May 30, death on 92nd day.

Rabbits 93 and 115, which survived their meningitis so long, showed the usual initial fall in weight to a minimum between the 12th and 20th days, to rise again to the preinfection figures, and remain there with only slight variations until the last few days.

SURVIVAL AND RECOVERY

Perhaps the most interesting point upon which we hoped to throw light was whether the superinfected rabbit suffering from a bovine tubercle bacillus meningitis will, under any circumstances, throw off the disease and recover. A second point was to what extent the size of the intrameningeal dose affects the survival of both the superinfected and control rabbits. Our results from these angles were very interesting (table 1).

First, it developed that with a *relatively large dose*, intrameningeally, the rabbits all die of meningitis, and the superinfected animals at least as early as, if not earlier than the controls. Our impression is that the superinfected animals die earlier with the larger dosages and show more extensive meningeal lesions. Our actual figures are as follows: When employing 0.0005 gm. of B1 intrameningeally, 4 superinfected animals of series III died or were moribund on the 9th, 11th, 12th and 15th days, all of them paralyzed and with marked macroscopic lesions of the cerebral meninges. Four corresponding controls died on the 12th, 12th, 16th and 38th days respectively, also paralyzed and with a similar degree of meningitis macroscopically. (The microscopic study of the brains, still to be made, may prove of interest.)

Next, it was found that with a *medium-sized dosage of* B1 intrameningeally (0.00002 gm.), again all rabbits died, but with a marked difference in the period of survival as between superinfected and control animals. In series VIII all 5 control animals died almost simultaneously, on the 18th, 20th, 21st, 23rd and 23rd days respectively. The 5 superinfected animals, on the other hand, survived an average of forty-two

days, the periods being 27, 29, 39, 56 and 59 days respectively. In series VII the same dosage of 0.00002 gm. of B1 was used. All 3 controls were dead by the 24th day. Of the three superinfected rabbits one was moribund on the 9th day, an immediate severe reaction, a second died on the 22nd day, and the third, no. 93 (table 2), threw off its infection and

TABLE 1

Experimental tuberculous meningitis: Survival after meningeal infection

PRIMARILY INFECTED					SUPERINFECTED			
Number	Mode of death	Period of survival	Remarks		Number	Mode of death	Period of survival	Remarks
		days					*days*	
36	Died	12		*Series III*	33	Killed	9	Moribund
32	Died	12		0.0005 gm. bovine bacilli	39	Killed	11	Moribund
38	Died	16		intrameningeally	31	Died	12	
34	Died	38			35	Died	15	
110	Died	18		*Series VIII*	107	Died	27	
104	Died	20		0.00002 gm. bovine bacilli	105	Died	29	
108	Died	21		intrameningeally	101	Died	39	
102	Died	23			109	Died	56	
106	Died	23			103	Died	56	
96	Killed	18	Moribund	*Series VII*	91	Killed	9	Moribund
92	Died	21		0.00002 gm. bovine bacilli	89	Died	22	
90	Died	24		intrameningeally	93	Died	328	
116	Died	32		*Series IX*	115	Killed	173	Moribund
112	Died	33		0.000004 gm. bovine bacilli	111	Died	92	
118	Died	39		intrameningeally	117	Killed	95	Moribund
114	Died	59			113	Died	238	
122	Died	27	Ether	*Series X*	121	Died	54	Ether
126	Died	32		0.000004 gm. bovine bacilli	123	Died	5	Ether
130	Killed	59	Moribund	intrameningeally	127	Killed	79	Moribund
128	Died	65			125	Killed	106	Moribund
124	Killed	74	Moribund					

apparently recovered, only to relapse in the 9th month and finally die, paralyzed, on the 328th day.

Up to this point we were seeking a dosage of bovine bacilli which would regularly cause death of the controls and permit the superinfected rabbits to survive. We tried one-fifth of the previous dosage, and with this amount of 0.000004 gm. of dried bovine bacilli intrameningeally

thought for some time that we had attained our goal. A glance at the chart will show how in series IX the 4 control animals died on the 32nd, 33rd, 39th and 59th days respectively, while of the 4 superinfected animals, 2 died on the 92nd and 95th days respectively, while the third, no. 115 in table 2, was killed moribund on the 173rd day and no. 113 survived 238 days.

By the fortieth day after beginning series IX, three of the 4 controls were dead, and the superinfected animals bade fair to survive as had rabbit 93. We therefore injected another series, X, with the same quantity, 0.000004 gm. of B1 intrameningeally.

With this group we were unfortunate, since one control and two of our 4 superinfected animals died apparently from ether. The two which eventually died of meningitis lived long enough, however, to demonstrate that they too possessed considerably more resistance than the controls.

It is seen that we have not yet accomplished what we set out to do, namely, to demonstrate that the sensitized rabbit will completely throw off the same virulent bovine-bacillus infection of the meninges that kills the nonallergic control. But we are convinced that it is only a matter of yet smaller dosage. Already new animals have been started, but the time required to settle the point renders it advisable to publish the results thus far obtained.

CEREBROSPINAL FLUID

Cell Counts

When it was found that 0.1 to 0.3 cc. of cerebrospinal fluid could be withdrawn, from time to time, by puncture of the occipito-atlantoid ligament, the study of cells in the fluid became of paramount interest. Such study should definitely establish the fact of infection of the meninges; it should also throw further light on the question of the difference in immediate and ultimate response to infection on the part of the allergic as compared with the nonallergic animal.

Normal red and white cell counts: In the beginning we limited our cell counting to the white cells. Then, when blood-tinged fluids were occasionally obtained, we felt that the red cells should also be counted, with a view to determining whether faulty technique was drawing blood to the extent of marring our white-cell counts. Finally, we came to the conclusion that a few fluids, usually in the early response to superinfection, or not long antemortem in the controls, are definitely bloody.

We found, as a matter of fact, that even under ordinary circumstances red cells are practically always present in the spinal fluid, and are in proportion to the number of white cells to the extent that the two types are usually high or low together. In normal fluids, withdrawn before any infection of the meninges whatever, we found from 0 to 480 red cells per cu. mm.; only once were there no red cells at all. One group of 6 rabbits showed red-blood cells 0, 34, 40, 44, 64, 120, as against white-blood cells 5, 24, 14, 34, 18 and 10 respectively. It should be added here that we have made spinal fluid white-cell counts in 22 normal rabbits. All counts were under 50 cells except one count of 86, probably due to an unnoted admixture of blood. Five counts were under 10 cells, 8 counts from 10 to 20 cells, 5 counts from 20 to 30 cells, one count of 33 cells, another of 34, and one count of 46 cells. On the basis of these counts we should regard the normal limit of white cells in the rabbit's cerebrospinal fluid to be certainly not higher than 50 per cu. mm.

Kasahara (3) has recently published a paper on experimental tuberculous infection of the rabbit's meninges. Bacilli were introduced through the occipito-atlantoid ligament. The infections were, however, exclusively primary. His counts in normal animals were lower than ours, namely, 0 to 10.

White-cell counts in presence of tuberculous meningitis: If now we turn to the tables of white-cell counts, there is noted, first of all, a rather striking difference between those of the two sets of rabbits during the first twenty-four and forty-eight hours. On the superinfected side (table 2) the counts are almost uniformly high, there being only one exception among twelve counts. On the other hand, while the results among the controls (table 3) are not so uniform, there are, nevertheless, only three counts among thirteen which are up to 2000 during the first forty-eight hours. Furthermore, if we note the few counts on the third, fourth, and fifth days, the discrepancy continues the same.

Next it is observed that the course of the white-cell counts, during the progress of the meningeal disease, shows interesting variations. Of superinfected animals going on to temporary recovery with later relapse, and in which the counts are fairly complete, there are two, nos. 93 and 115. Both show the same cell-count course, that is, they begin with the initial intense reaction and then gradually decrease toward normal. Rabbit 111 bade fair to run a similar course, inasmuch as its weight was maintained and the white-cell count of the cerebrospinal fluid was steadily falling through the 41st day after meningeal infection. Then, on the

TABLE 2

Experimental tuberculous meningitis: Spinal-fluid cell counts: Leucocytes of superinfected animals

NUMBER	DAYS AFTER MENINGEAL INFECTION																	REMARKS
	1	2	5	10	14	18	28	37	49	62	74	81	95	116	173	238	276	
43				4,170														Killed 9th day, moribund
61			4,650															Killed 4th day, moribund
69					1,800													Killed 14th day, moribund
75										1,450								Killed 62d day, moribund
71														230				Died 236th day
73										1,075								Killed 67th day, moribund
77													1,620	128				Killed 250th day, by dog
83	4,660																	Died 1st day, with ether
85	2,230		5,190		7,280													Died 14th day
89		3,640		734		2,110												Died 22d day
93		6,720		1,394		905				120			82		29		90	Died 328th day
103	754			1,360														Died 56th day
105	2,260																	Died 29th day
107		2,160																Died 27th day
109		2,860			1,280													Died 56th day
111		7,940			1,070	810	570		230		2,410	4,660						Died 92d day
113					50	50			24							130		Died 238th day
115	5,060			1,780		1,890	610	390	270		240				110			Killed 173d day, moribund
117		3,630		7,980		1,010		250	310		240	270	390					Killed 95th day, moribund
121			5,620				680	300	590									Died 54th day, with ether
123			1,060															Died 5th day, with ether
125							480	110										Killed 106th day, moribund
127		5,060						290										Killed 79th day, moribund

TABLE 3

Experimental tuberculous meningitis: Spinal-fluid cell counts: Leucocytes of primarily infected animals

NUMBER	DAYS AFTER MENINGEAL INFECTION														REMARKS
	1	2	3	5	9	11	14	18	26	27	32	39	41	54	
50					3,660										
90		755				992		630							Died 24th day
92		123				652		2,730							Died 21st day
96			1,015			2,610		805							Died 18th day
102						2,490									Died 23d day
104		980				2,890									Died 20th day
106		2,460													Died 23d day
108	640														Died 21st day
110	944														Died 18th day
112	1,320					4,620		4,090	1,680						Died 33d day
114							2,600			720			710		Died 59th day
116		1,016				1,960		3,230							Died 32d day
118		830					6,200								Died 38th day
122	2,430									2,560					Died 27th day, by puncture
124		2,410								715		530		630	Killed 76th day, moribund
126		1,080													Died 32d day
128				215							1,410	1,780		1,640	Died 65th day
130	440			360							2,450	1,710		940	Killed 59th day, moribund

74th day, it was found that the white-cell count had remounted to 2410, and loss of weight became progressive. A further count of 4660 on the 81st day confirmed the previous high count. By this time the animal had begun to show weakness in the hindquarters, and on the 92nd day was found dead. Here we must reason that at some time between the 41st and 74th days an autogenous superinfection took place which overwhelmed the animal's resistance. On the other hand, Rabbit 117 of the same series changed from a favorable to an unfavorable case about the 74th day without any marked increase in the white-cell count.

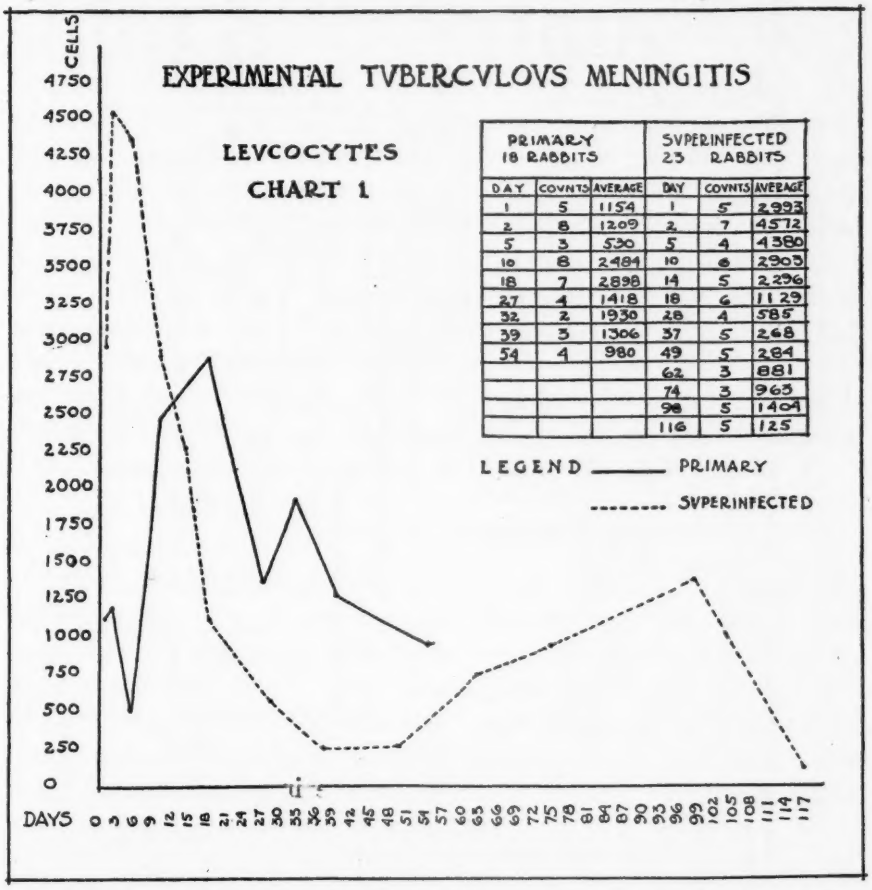
One rabbit, no. 113, ran a very unusual series of spinal-fluid cell counts. An accident befell the count immediately after meningeal infection and no count was made until the 14th day. It was then 50 white cells and 200 red cells. A second count on the 21st day again showed 50 white cells, and a third on the 48th day showed 24 white cells. We concluded that this rabbit had not received its dose of B1 into the meninges, and that no meningitis had existed. The animal continued apparently normal for seven months, when to our surprise it showed a little weakness behind and was found to be losing weight. A little later it gave a cerebrospinal-fluid count of white blood cells 130 and red blood cells 70, and on the 238th day after meningeal infection died, with an almost complete paralysis of the hind legs.

When we turn now to the counts in the control animals, in which the meningeal infection was primary, there seems to be no great uniformity beyond that of low counts with the initial response to infection. It may be stated, however, that most of the control animals showed high counts during the period of the 11th to the 18th day after meningeal infection. Furthermore, the fact was very striking in the controls of series IX that 3 of the 4 animals, not long prior to death, showed a phenomenon never observed in the superinfected animals late in the disease, namely, a bloody fluid clotting almost immediately on removal. Autopsy of these animals showed definite hemorrhagic exudate underlying the medulla and pons in two cases.

Curves were plotted of the white-cell counts in the cerebrospinal fluid of the two sets of rabbits (chart I), in order to visualize better the difference in response to the meningeal infection. If we study first the curve of the primarily infected animals, there is noted the relatively mild early response; not until about the 5th day does the curve begin to ascend. Meanwhile, we may reason that the meningeal infection with B1, primary in these animals, is rendering the rabbits increasingly

allergic up to the third week. By the latter time the counts have risen, and they reach their maximum during this period of maximum allergy. From now on the counts tend to fall as the animals gradually succumb.

In the curve of the superinfected rabbits there is noted the immediate response, reaching its maximum during the first five days and then falling steadily. The secondary rise in the counts of these animals is



PRIMARY 18 RABBITS			SVPERINFECTED 23 RABBITS		
DAY	COVNTS	AVERAGE	DAY	COVNTS	AVERAGE
1	5	1154	1	5	2993
2	8	1209	2	7	4572
5	3	530	5	4	4380
10	8	2484	10	6	2903
18	7	2898	14	5	2296
27	4	1418	18	6	1129
32	2	1930	28	4	585
39	3	1306	37	5	268
54	4	980	49	5	284
			62	3	881
			74	3	965
			98	5	1404
			116	5	125

occasioned by the recurrence of the high counts in the rabbits, which seemed to be on the road to recovery and then apparently underwent an autosuperinfection of their allergic tissues. These curves were based on 107 white-cell counts of the cerebrospinal fluid of 18 primarily infected and 23 superinfected rabbits.

Red-cell counts: Red-cell counts were made only in series IX and X. It is noteworthy that all the strikingly high red-cell counts during the

TABLE 4

Experimental tuberculous meningitis: Spinal-fluid cell counts: Red cells of primarily infected animals

NUMBER	DAYS AFTER MENINGEAL INFECTION												REMARKS
	1	2	3	5	11	14	18	26	27	34	41	54	
112	2,700				4,600		2,900	230					Died 33d day
114						1,220			80		12,000		Died 59th day
116		2,400			4,100		4,400	14,000					Died 32d day
118		3,000				8,500				4,040			Died 39th day
122	1,380								160				Died 27th day, by ether
124		1,420							6,800	290		390	Killed 79th day, moribund
126		360											Died 32d day
128				860						2,640	1,260	1,020	Died 65th day
130	4,440			1,110						69,550	870	900	Killed 59th day, moribund

Red cells of superinfected animals

NUMBER	DAYS AFTER MENINGEAL INFECTION													REMARKS
	1	2	5	11	18	25	35	41	49	74	81	95	238	
111		22,800			1,760	310	390	510		2,250	290			Died 92d day
113					200	1,820			110				70	Died 238th day
115	17,100			3,400	2,200	660	730							
117		6,500		7,200	1,660		1,060		390	280	130	750		Killed 95th day, moribund
121			66,300			6,100								Died 54th day, with ether
123			960											Died 5th day, with ether
125							1,850							Killed 106th day, moribund
127		17,020		12,400		430		140						Killed 79th day, moribund

first five days occurred in the superinfected rabbits. In the superinfected animals which recover, the red cells diminish, as do the white cells. In the control rabbits, on the other hand, the high red-cell counts, when present, are found usually toward the time of death. In a number of these control rabbits a fibrin clot formed almost immediately and made exact cell counts impossible, as mentioned before (table 4).

Differentials: Differential counts were made on most of the fluids of series IX. They showed always a high lymphocytosis, below 90 per cent only six times among 23 differentials, 89 per cent four times, and 85 per cent twice. Polymorphonuclears never were high, the maximum being 5 per cent. What difference there was in polymorphonuclears during the first forty-eight hours was in favor of the superinfected animals, 3 of them showing respectively 4, 4.25 and 4 per cent, as against 1, 0.5 and 1 per cent in the 3 parallel controls. On the other hand, 2 superinfected rabbits of another series, given 0.00005 gm. intrameningeally, showed at the end of twenty-four hours respectively 47 and 12.5 per cent polymorphonuclears. It is entirely possible that larger intrameningeal doses would bring out more marked differences in the spinal-fluid differential counts as between superinfected and control animals. Further work is being undertaken to clear up this point.

Lysis of Bacilli in Spinal Fluid

Tubercle bacilli were sought in 13 spinal fluids from superinfected rabbits and in 7 from primarily infected rabbits. The period after meningeal infection varied from twenty-four hours to sixty-seven days. No appreciable difference could be made out. Bacilli were found in 8 of the 13 superinfection fluids and in 3 of the 7 primary-infection fluids. The number of bacilli was practically the same, and no difference was noted in their staining qualities. We also plan to go into this question more thoroughly in further experiments.

PATHOLOGY

Thus far pathological study of the animals has been limited to the gross. With regard to the brain lesions it was found that the method of infection, by puncture of the occipito-atlantoid ligament, with our relatively small doses resulted almost always in a pathological process restricted, macroscopically at least, to the meninges of the under surface of the pons and medulla. Presumably this process continued down into

the meninges of the cord, but this latter point was not determined. It was striking that, with the relatively small doses of series IX and X, almost no tubercles were visible to the naked eye. Only 2 of the 13 animals of these two series showed definite tubercles in the cerebral meninges, and such tubercles as were seen were very few in number and small in size. A definite exudate, usually of brownish color and more or less organized, was, on the other hand, always present, underlying the pons and the medulla. With series VII and VIII, in which somewhat larger doses were used, tubercle formation was more often visible macroscopically, namely, in 8 of 15 brains. Again, in series III, infected by the postorbital route with still larger dosage, macroscopic tubercle formation was always present in large amount, and about the optic chiasm as well as further posteriorly.

As to extension of disease to the lungs and other organs, it was found that the smaller infections remain, to a large extent, limited to the meninges. Of series VII, VIII, IX and X, comprising 29 animals, none showed additional tuberculosis of organs other than the lungs and only 9 showed macroscopic tubercles in the lungs. Even here the tubercles were never in any great number, and no marked difference in this respect could be made out between superinfected and control rabbits.

DISCUSSION

The most striking result of these experiments is the fact that tuberculous infection of the meninges, always regarded as peculiarly and almost uniformly fatal, obeys, in our experimental animals at least, the same laws as do the peritoneum, pleura and various organs. We find that in the meninges allergy is a two-edged sword, as in other tissues, possibly hastening death with the relatively large dose, protecting to a marked though relative degree with a medium dose, and probably enabling the animal to completely throw off infection with the small dose. The thirty odd authentic cases in the literature of man's recovery from tuberculous meningitis may here find confirmation, and, in so far as animal experimentation may be applied to human beings, one feels that much more human tuberculous meningitis would recover were it not so often but the dominant manifestation of a general miliary disease. Also, the clinically interesting surmise presents itself that the ordinary human case of advanced tuberculosis may well undergo slight infections of the meninges from time to time, enough to cause headache and suspicions of

meningitis, but not enough to warrant lumbar puncture, and ultimately adjudged as not being meningitis through the very fact of recovery.

The great importance of the quantity of bacilli producing the superinfection is again brought out strikingly. While the rabbit with a quiescent and localized tuberculosis succumbs quickly to 0.0005 gm. of dried virulent bovine bacilli in the meninges, it survives 0.00002 gm. three times as long as the controls and may survive 0.000004 gm. as long as 238 days.

As to the difference in the initial reaction as between the superinfected and the normal control animal, the results here are the more demonstrative because the rabbit is notoriously sluggish in all the reactive phenomena of allergy.

The weight curve is of considerable interest. The superinfected rabbit, while throwing off its meningitis and apparently entitled to lose considerable weight, nevertheless maintains it surprisingly well. The control animal, as its disease progresses, loses weight rapidly and steadily, faster indeed than one would expect with the infection practically limited, as it is, to the meninges.

CONCLUSIONS

1. The phenomena of allergy and superinfection manifest themselves in the meninges of the rabbit apparently just as in other organs and serous membranes of various experimental animals.

2. The size of the superinfecting dose is of the greatest importance, although presumably not the only determining factor. With relatively high doses of dried bovine tubercle bacilli intrameningeally, death is probably hastened by allergy; with medium sized doses of bacilli the period of survival is about double that of the control; with relatively small doses the superinfected animals often appear to throw off their disease temporarily and survive a long period in comparison with the control. The latter dies of meningitis fairly early.

3. Spinal-fluid examinations indicate an immediate meningeal reaction considerably more intense on the part of the superinfected rabbit as compared with the control. Spinal-fluid cell counts in the superinfected animal, both white and red, are high during the few days immediately following meningeal infection, and gradually diminish as the animal resists the disease. The spinal-fluid cells of the control animal, on the

other hand, begin relatively low and then follow an irregular course upward.

4. The weight of the superinfected rabbit is surprisingly well maintained while the animal is combating the meningitis. The loss of weight in the progressively failing control is in marked contrast.

5. Lysis of tubercle bacilli as an important factor in the elimination of tuberculous superinfection requires further study. Our results would indicate that bacteriolysis is far from complete.

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THE INFLUENCE OF HYPERCHOLESTERINAEMIA ON EXPERIMENTAL TUBERCULOSIS OF THE RABBIT[1]

RICHARD H. JAFFÉ AND SAMUEL A. LEVINSON

The tubercle, as the specific reaction of the body to tubercle bacilli, determines the fate of the infection. It depends mainly on the activity and viability of the cells which form the tubercle, whether the infected area is walled off and the process comes to a standstill, or whether the bacilli overcome the zone of cellular defense and invade new parts of the body. The cells, stimulated by the diffusible toxic products of the virus to grow and to proliferate, are continuously in the stage of abnormal irritation that is evident from their increased permeability (W. F. Petersen). This irritation will probably affect their specific functions, increasing or diminishing them as compared to the original cells from which they are derived. Which are these original cells, and what are their normal functions?

It is a well-established fact that the most characteristic elements of the tubercle, the epithelioid cells, originate in certain types of cells widely distributed in the body and united now in the so called *reticulo-endothelial* system of Aschoff (1). Many investigations have shown that the reticulo-endothelial cells have distinct functions (Jaffé (2)). They play an important rôle in the iron and cholesterol metabolism (Eppinger (3), Rothschild, Landau and McNee (4)), they are undoubtedly connected with processes of immunization (Bieling and Isaac (6), Standenath (7), Siegmund (8), Gay and Clark (8a), etc.), they possess a great ability to phagocytose, and they show a strong affinity for vital stains (Kiyono (9)).

Regarding the cholesterol metabolism, it has been found that an increase of cholesterol in the blood under certain conditions is followed by the storage of double refracting cholesterol compounds in the reticulo-endothelium (Anitschkow (10), Chalatoff (11)). This is especially true of the herbivorous animals (rabbit, guinea pig).

The question arises, whether the epithelioid cells descending from the

[1] From the Department of Pathology of the University of Illinois College of Medicine, the Laboratory of the Municipal Tuberculosis Sanitarium, and the Uihlain Memorial Laboratory of the Grant Hospital, Chicago.

reticulo-endothelial cells are still able to take part in the accumulation of an excessive amount of cholesterol in the blood. Should cholesterol be deposited in the epithelioid cells of the tubercle, it may influence the course of the infection, because cholesterol has often been brought into connection with infectious processes.

In acute infectious diseases the cholesterol content of the blood is decreased (Chauffard, Laroche and Grigang (12), Stepp (13), Leupold and Bogendoerfer (14)); and, also, advanced cases of tuberculosis usually show a low amount of cholesterol in the blood (Bacmeister and Henes (15), Chauffard (16), Weltmann (17), Eisler and Laub (18), Rosenthal and Petrzak (19), Sweany, Weathers and McCluskey (20)). The same authors point out, however, that in early stages, or in mild cases, the cholesterol of the blood may be found normal. Henning (21) concludes from his cholesterol studies in tuberculosis that the cholesterol, during the course of the infection, is transformed into an unknown substance closely related to it. He further considers it possible that this lipoid participates in the defensive reactions of the body.

Leupold and Bogendoerfer were able to increase the resistance of laboratory animals to experimental infections and to intoxication with diphtheria toxin by feeding cholesterol. They attribute a protecting power (fixation of the toxins?) to the cholesterol, because it does not possess bactericidal properties and diminishes phagocytosis. (See also Dewey and Nuzum (22).) Tunicleff (23) found that dilutions of cholesterol, 1:100, reduced phagocytosis, while dilutions of 1:500 to 1:2000 promoted it. Beumer (24) also noticed a protecting action of the cholesterol in guinea pigs injected with diphtheria toxin. He supports the statement that the deposits of cholesterol in the reticulo-endothelial cells may increase the resistance of the body. Bersani (25) observed good results of intramuscular injections of cholesterol dissolved in oil in patients suffering from tuberculosis.

The cortex of the adrenal is characterized by a high content of cholesterol and cholesterol esters, which show fluctuations corresponding to that of the cholesterol of the blood (Wacker and Hueck (26), Landau (27)). The high cholesterol content of the adrenal is said to cause the great resistance of this organ to tuberculosis (Mauriac (28)). According to v. Hansemann (29), decrease of the lipoids renders this organ susceptible to tuberculosis. Because the blood cholesterol is low in active tuberculosis, and the amount of cholesterol in the suprarenals is determined by that of the blood, the microscopic and chemical examination of the

adrenals in tuberculosis usually yields low figures of this lipoid (Landau (30), Chauffard (31), etc.)

These observations, and the facts known about the relations of the reticulo-endothelial cells to the formation of the tubercle and to the cholesterol metabolism, suggest the study of the anatomical picture and of the course of tuberculosis in animals artificially kept in a stage of chronic hypercholesterinaemia.

We chose for our experiments rabbits, in which hypercholesterinaemia can be easily produced. Adult rabbits were fed daily, by means of a soft rubber tube, with pure cholesterol dissolved in cottonseed oil (0.25 gm. cholesterol in 5 cc. oil), or with egg-yolks (one egg-yolk each day) or with plain cottonseed oil (5 cc.). The oral administration of the cholesterol gives the most constant results. Intravenous or intraperitoneal injection of cholesterol suspensions, as used by Dewey (32), are less reliable, because the amount of cholesterol which can be introduced by this method is too small. Subcutaneous injections lead to deposits of cholesterol with mere local cellular reactions (Basten (33), Stewart (34)).

After two months' feeding the chemical examination of the blood revealed a marked increase of the blood cholesterol in the animals treated with cholesterol oil and egg-yolk. Two animals of each group were now infected by intravenous injections of a suspension of 20 mgm. of bovine tubercle bacilli (strain 6–30–18) in physiological salt solution (2 cc.). Two animals in each group were saved as feeding controls. In addition, two normal rabbits, which received the usual laboratory diet (carrots, oats and bread), were subjected to the same infection as the cholesterol rabbits.

The feeding of the animals with cholesterol oil, egg-yolk and plain oil was continued for three months. In this time a pronounced tuberculosis had developed in the controls. Then all the animals were killed by ether on the same day. Liver, lungs, spleen, adrenals, kidneys, lymph nodes and different blood-vessels were immediately fixed with 10 per cent formalin and with 80 per cent alcohol. Frozen sections were made of the material fixed with formalin and stained with hematoxylin-eosin, sudan III, hematoxylin and nile-blue-sulphate. Unstained sections were mounted with glycerin-gelatine for examination of double refracting fat. In some instances the methods of Lorrain-Smith-Dietrich for lipoids, and of Fischler for fatty acids, were used. The material fixed in alcohol was imbedded in paraffin and stained with hemalaun-eosin,

methyl-green-pyronin and carbol-fuchsin-methylene-blue for tubercle bacilli.

CHEMICAL EXAMINATION OF THE BLOOD

Before entering into the main topic of our present study, namely, the microscopic examination of the tissue changes, the findings on the blood cholesterol may be summarized briefly.

Blood was drawn at regular intervals from the ear-veins of the rabbits, and the cholesterol was determined in the whole blood, as well as in the plasma, by the method of Bloor. Kaolin was added to the alcohol-ether mixture to remove any trace of coloring matter that might interfere with the reading in the colorimeter.

The average normal cholesterol content of the whole blood of the rabbits used in our experiments was between 80 and 90 mgm. per 100 cc. The feeding of pure cottonseed oil caused a slight increase of the cholesterol after 3 or 5 months. The highest value found after 5 months was 144 mgm.

The tuberculous infection in the control rabbits, kept on the usual laboratory diet, led to a rise of the cholesterol to 115–130 mgm. This increase continued in one animal until it was killed. The cholesterol went up to 140 mgm. In the other rabbit the cholesterol went down during the last weeks of its life, being finally slightly higher than at the beginning of the experiment (100 mgm.).

The blood-cholesterol of the cottonseed oil-fed rabbits, which received tubercle bacilli, was 85 mgm. at the time of the infection. There was a very pronounced increase subsequent to the infection, which reached a climax of 264 mgm. after one month. The last examination, 5 months after the experiment had been started, showed 134 mgm.

The blood of the cholesterol cottonseed oil-feeding controls contained after 2 months' feeding 250 mgm., and after 5 months, 833 mgm. cholesterol per 100 cc. (average of the two rabbits). The average of the egg-yolk-feeding controls after 2 months was 330 mgm., and after 5 months 508 mgm.

The animals which received cholesterol-oil and which, after 2 months' feeding, were injected with tubercle bacilli, showed a marked rise of the blood-cholesterol following the infection. The cholesterol rose from 250 to 488 mgm. within 3 weeks. But, as the feeding continued, the increase of the cholesterol was only slight; and the final examination of the blood, 3 months after the tubercle bacilli had been injected,

revealed 558 mgm. of cholesterol per 100 cc. It seemed as if the progression of the tuberculosis had an inhibitory effect on the further increase of the cholesterol content of the blood. This was even more evident from the experiment with egg-yolks. Three weeks after the infection the blood contained 242 mgm. cholesterol, and the same amount was found two months later, whereas in the egg-yolk controls the cholesterol rose in the same time very distinctly from 330 to 508 mgm.

The storage of the lipoid in the tuberculous lesions, evident from the microscopic examination, does not fully explain the diminution of the accumulation of the cholesterol in the blood-stream. We believe the resorption of the fat from the intestinal content into the blood-stream to be impaired when the infection becomes more severe.

The rise of the blood-cholesterol, which constantly follows the injection of tubercle bacilli, needs further investigation. Other infections of the rabbits, for instance, with paratyphoid bacilli, are known to lead to an increase of this lipoid (Gorter and ten Bokkel Huinink). It is probable that the disintegration of cells causes this finding. The hypercholesterinaemia observed in starvation, according to Okunoff, is due to the breaking up of the protoplasm of cells rich in cholesterol.

The results of the examination of the plasma were similar to that of the blood.

HISTOLOGICAL PART

It seems wise to report, first, on the changes found in the animals which were fed only with the lipoids, without the animals being infected. Then the findings in the tuberculosis controls will be described, especially with regard to the fatty changes in the tuberculous lesions. This information is no doubt necessary for an interpretation of the changes in the main groups of our experiments.

I. Cholesterol-Cottonseed-Oil Controls

The animals in this group behaved like the normal controls. We did not determine the blood-pressure, but through other investigations it has been found that the feeding of cholesterol leads to hypertension (Schnidtmann (37), Schoenheimer (38)). The corneas of one rabbit showed the peripheral cholesterol ring described by Versé (39). The necropsies revealed the lipoid deposits in the intima of the aorta, mainly in its thoracic part, so much resembling human atheromatosis (Anitschkow (40), Bailey (42), Chuma (43), Knack (44), Schoenheimer). Besides

these in the aorta we found marked cholesterol infiltrations forming circumscribed placques in the pulmonary artery and its larger branches, and in the splenic arteries. No vascular changes were noted in the liver, kidney, etc.

The liver was pale yellowish-brown and soft. The liver cells were filled with large and small double refracting fat droplets. The fatty changes were usually more pronounced at the periphery and in the centre of the acini than in the intermediate zone, which was almost free from fat. The Kupffer cells in all parts of the liver were laden with anisotropic fat granules and droplets. The fat-carrying cells frequently appeared enlarged, and their nuclei showed irregular forms. No fat was present in the epithelial cells of the bile-ducts. According to Chalatoff, the use of sunflower-oil seems to be essential for the production of fatty infiltration of the biliary epithelium. There were accumulations of round cells and single fat-containing cells in the connective tissue about the bile-ducts, but we did not find cirrhotic changes or proliferation of the bile-ducts, as mentioned by Chalatoff, Bailey and Chuma. The latter author used lanolin in his experiments. The proliferation of the bile-ducts was also missed by Dewey and Schoenheimer. Dewey and Chalatoff observed concretions of cholesterol in the gall-bladder. Such concretions were not found in our animals, and the bile was always clear, thin and yellowish-green.

The number of lipoid cells in the spleen was variable and rather small. Dewey, Weltmann and Biach (45) and Bailey had the same experience. Zinserling (46) stated that infiltration of cholesterol esters appears late in the cells of this organ. We found the double refracting fat droplets in isolated cells of endothelial or reticular type, or in single larger elements, lying free in the sinus, as described by Anitschkow. Fatty changes of the arteries, however, were always very distinct, and involved the intima, as well as the adjacent muscle cells of the media. Finally, an increase of blood-pigment and many pseudo-eosinophilic leucocytes and myelocytes should be mentioned (Schoenheimer, Anitschkow).

The behavior of the lungs is of special interest for the purpose of our investigations. Apart from the larger branches of the pulmonary artery, double refracting fat droplets in this organ are limited to single flat cells in the alveolar septa. These cells usually lie outside the capillaries, closely attached to their wall. The endothelial cells never contain fat, though the plasma filling the lumina of the capillaries frequently stains yellow with sudan III. In a few vessels, isolated monocytes with

small lipoid granules in their protoplasm could be noted. Similar observations have been reported by Chuma and Zinserling. In only one case did we see a larger number of fat-cells in the pulmonary capillaries. In this case cholesterol-oil was found in the alveoli of a circumscribed area. The oil had apparently been brought in accidentally. The fat was partly engulfed by very large round or oval cells with indistinct outlines and small pyknotic nuclei. The fat in the alveoli did not give double refraction, except a few intracellular droplets. The accumulation of fat-containing cells in the alveolar capillaries was undoubtedly due to the fat being carried away from the alveoli by means of phagocytosing wandering cells. Similar pictures are seen in the capillaries of the lactating mammary gland (Gruber (47)).

The kidneys of one of our cholesterol control rabbits showed bright, yellowish-white radial stripes on the cut surface. They were 3 to 5 mm. long and 1 or 2 mm. broad, and were located in the peripheral part of the medulla. Small depressions were found on the surface, corresponding to the glittering structures of the medulla. The microscopic examination revealed that the stripes contained an enormous amount of anisotropic material. In the centre there were large needles, which stained pale yellow with sudan III, and grayish-red with nile-blue-sulphate. The needles were surrounded by large cells filled with fat droplets, which appeared partly purple and partly violet in the sections stained with nile-blue-sulphates. Round cells were present in the periphery. Analogous findings were obtained in two of the cholesterol-tuberculous animals.

Bailey and Schoenheimer described similar changes, and supposed them to be cholesterol deposits in preëxisting interstitial lesions, probably due to an irritating action of the oil, used for dissolving the cholesterol, upon the tubuli (Schoenheimer). By comparison with changes observed in other cholesterol rabbits, but less pronounced than those just mentioned, we received the impression that the cholesterol infiltrations took place in the endothelial cells of lymph-vessels (see also Bailey). Interstitial inflammatory changes, producing disturbances of the lymph circulation, might have caused the enormous increase of the cholesterol infiltration in some of the animals. It is known that stagnation of the lymph favors the xanthoid transformation of tissue (Lubarsch). We were not able to decide whether the interstitial inflammation was the result of the oil-feeding, or belonged to the large group of the spontaneous kidney changes of the rabbit.

Besides the lipoid deposits in the medulla, single fat-carrying cells were found in the *interstitium*, and sometimes in the tufts of the glomeruli. Of the tubular epithelium, only that of Henle's loop sometimes contained fine isotropic and anisotropic fat granules.

In the mesenteric lymph nodes the lining endothelial cells of the sinus showed double refracting fat droplets. These cells sometimes appeared enlarged and desquamated. The reticulum cells also were often full of fat. In the thoracic lymph nodes these changes were only slight (see also Anitschkow).

A characteristic feature of experimental hypercholesterinaemia is the enlargement of the adrenals (Landau, Sternberg (48), Bailey, Schoenheimer, Zinserling). This hypertrophy of the adrenals was also observed in our experiments, and found to be due to an increase of cortical tissue. The weight of the adrenals surpassed the normal weight of the adrenal by only 15 to 20 per cent, though the size was almost double the normal. The cells of the cortex were markedly distended, and their protoplasm was pale and foamy. The nuclei appeared shrunken and dark, and with notched edges. Between the crossed Nicols of the polariscope a broad glittering band was visible, full of granules and crystals of different sizes. The larger crystals were predominant, and the cloudy masses of very small anisotropic granules typical of the suprarenal cortex of the normal rabbit were extinguished by coarse matter. The *zona glomerulosa*, almost free from double refracting fat in healthy rabbits, contained many optically active needles and droplets. In the internal part of the cortex a few lipoid granules were found in the endothelial cells of the capillaries. Kiyono and Aschoff have included these cells into the reticulo-endothelial system, because of their distinct affinity for vital stains and iron (Lubarsch (49)).

No advanced degeneration of the cortical cells of the adrenals was present in our rabbits, the time of feeding apparently being too short.

II. Egg-Yolk Controls

The changes found in the animals which had received egg-yolks were similar to those just described. But it may be stated that, as a whole, they were less pronounced. Particularly the amount of double refracting lipoids in the reticulo-endothelial cells was considerably smaller. In the liver many Kupffer cells were free from fat. More fat was seen in the liver cells. Like Bailey, we did not observe the difference in the distribution of the liver fat that Chalatoff had noted, comparing the liver

changes after feeding cholesterol-oil with those after feeding egg-yolk. This author found most of the fat in the centres of the acini in the animals fed with egg-yolk.

III. Plain Cottonseed-Oil Controls

The introduction of cottonseed-oil had no marked effect on the microscopic picture of the organs examined. There was only an irregular fatty infiltration of the liver cells.

IV. Tuberculosis Controls

The rabbits of this group showed the anatomical picture of a subacute nodular tuberculosis. The lungs were the organs most affected, and contained numerous grayish nodules, 2 to 5 mm. in diameter, with yellow centres. Tubercles were also found in the thoracic lymph nodes, in the liver, and once in the spleen and kidneys. In the latter organs the tubercles were small; the adrenals were enlarged.[2] In one case their weight was 1.4 gm. (normal weight of adrenals of a rabbit of the same size is about 0.7 or 0.8 gm.). Miliary, grayish, translucent tubercles were detected on the cut-surface in the cortex. No special attention has so far been given to the experimental tuberculosis of the adrenals, apart from the direct injection of tubercle bacilli into these organs (Yataro Sumiyoshi (50)).

In discussing the microscopic findings we will confine ourselves mainly to the fatty changes. Most of the investigators, who have made the occurrence of fat in the tuberculous lesions the subject of their microscopic studies, state that the young submiliary and miliary tubercle is free from fat (Rosenthal (51), Vallillo (52), Joest (53), etc.). In older tubercles fat droplets are found in the epithelioid cells and giant cells of the centre. The appearance of intracellular fat is followed by necrosis. When the necrosis becomes more pronounced and a typical central area of caseation is formed, it is surrounded by a distinct ring of fatty infiltrated cells. Beyond this ring the living tuberculous tissue does not contain fat, while in the zone of caseation comparatively little fat is present (Joest, Wells (54), Vallillo, Herxheimer (55), etc.).

For the problems we are dealing with, the experience of Joest is important: namely, that the living tuberculous tissue is free from fat, even if

[2] Webb, Gilbert and Ryder (AMERICAN REVIEW OF TUBERCULOSIS, 1921, v, 266) mention enlargement of the adrenals in tuberculous guinea pigs.

found in a liver with abundant fatty infiltration. Joest says, "The fatty disintegration of the tuberculous cells is independent of the fatty changes which may take place in the surrounding tissue."

Corper (56) concludes, from his experiments of feeding tuberculous guinea pigs with sudan III dissolved in oil, that the fat of the tubercles is derived from the preëxisting lipoids of the degenerated cells, because it does not stain vitally with the fat-stain, as does the deposited fat of the food.

Chemical analyses of tuberculous tissue have been made by Schmoll (57), Wells (58), Caldwell (59), etc.[3] In this connection, only Caldwell's findings of a high cholesterol-content in bovine lymph-node and liver tuberculosis need be mentioned. The wall, and especially the cheesy parts of the lesions, showed an actual increase of this lipoid, as compared with normal tissue. This increase of cholesterol is typical for any kind of necrosis, and not only for that of tuberculous origin.

The papers we have referred to are based mainly upon material from human beings and of cattle. As is evident from our experiments, the histological examination of the tuberculous tissue of the rabbit for fat yields similar results.

In the small submiliary tubercles of the liver, lymph nodes and spleen, microscopically visible fat was absent. The same can be said about the isolated syncytia and giant cells found in the portal capillaries of the liver. In the lung, few flat cells containing fine fat granules were seen between the epithelioid cells which were free from fat. In the adrenals the tubercles were located in the mesial, and specially, internal part of the cortex. They were well demarcated from the surrounding tissue, and consisted of large and pale epithelioid cells, which could easily be distinguished from the spongiocytes of the cortex (fig. 5). In sections used for fat-stain, but few small fat droplets, poorly stained, were found in the epithelioid cells. There were single cells filled with larger fat droplets, some of them giving double refraction (fig. 4). These cells seemed to be cortical cells enclosed by the tubercle. It should be mentioned that the normal lipoid content of the cortex was not affected by the tuberculous process.

In the tubercles, which had passed through the stage of submiliary size, fat-carrying cells were found in the centres. As soon as the centre became necrotic, a sharply demarcated ring of fatty degenerated cells

[3] For a detailed discussion of this question see *The Chemistry of Tuberculosis*, Wells, DeWitt and Long, and paper by E. R. Long, *Bull. Johns Hopkins Hospital*, 1922, xxxiii, 377.

appeared about the necrosis. Fat droplets were also found in the necrosis itself. Their number was markedly diminished when the necrosis changed to caseation. The epithelioid cells in the periphery remained free from fat.

The fat of the perinecrotic zone and of the necrosis itself gave the microchemical reactions of neutral fat. It stained yellowish-red with sudan III, and pink with nile-blue-sulphate. Only a few small double refracting crystals were visible under the polariscope in the necrotic areas. The zone of intensive fatty metamorphosis, described above, appeared dark between the crossed Nicols. The method of Lorrain-Smith-Dietrich brought out single black granules in but a few sections. With Fischler's stain for fatty acids a negative result was obtained. Also, Fischler and Gross were not able to find microscopically free fatty acids in tubercles. Babes (61) saw a very small amount of fatty acid in tuberculous lesions of the human lung.

We have no exact microchemical method for determining free cholesterol, especially if it is intimately mixed with other substances (Wacker and Hueck). This will explain the difference between the results of the microscopic and chemical examinations of the tuberculous tissue.

A kind of lesion usually found in tuberculous lungs differs from typical tubercles in regard to the occurrence and chemical nature of the fat. In all stages of its development the epithelioid-cell tubercle is surrounded by a perifocal zone of cellular exudation into the alveolar spaces. The cells of the exudate are large, round or oval, with pale homogeneous or vacuolated protoplasm, and they resemble the epithelioid cells of the tubercle. The structure of the nuclei, especially, is quite similar. But these cells possess more distinct outlines and do not tend to form nodular accumulations, as do the cells of the tubercle. Besides, the alveolar septum does not seem to be altered, and there are no signs of beginning necrosis of the exudate. However, the cells contain much fat, which gives distinct double refraction, and seems to consist mainly of cholesterol esters.

The perifocal changes undoubtedly result from the diminished action of the tuberculous toxins, which become diluted and weakened in diffusing from the tissue of the tubercle.

The question arises as to the cause of the different cellular reaction. In the centre we find a proliferation of cells, which later is followed by isotropic fatty degeneration and necrosis. In the periphery, proliferation and anisotropic fatty degeneration go together. The difference of the concentration of the irritating toxin does not fully explain the differ-

ent microscopic picture; because then we should expect to find similar changes in the most peripheral part of the tubercles that borders on the alveoli with the cells filled with anisotropic lipoid droplets. As this does not hold true, the cells reacting differently to the same toxin would rather seem to be cells of different origin. In this connection, attention should be called to the investigations of French authors, who have found that the nucleated alveolar epithelial cells normally contain lipoid granules made up largely of free cholesterol (Faure-Fremiet (62)). We are, therefore, inclined to regard the cells with the anisotropic fat droplets in the alveoli about the tubercles as proliferated, desquamated and degenerated epithelial cells of the alveoli. Their readiness to undergo anisotropic fatty degeneration is explained by their normal content of free cholesterol.

In recent papers on the nature of the cells of pneumonic exudates, a tendency is noted to consider all the mononuclear cells found in the alveoli as derived from the endothelial cells of the capillaries or from the monocytes of the blood (see Permar (63) who most thoroughly reviews the literature). Observations like those just discussed indicate that this cannot be considered an absolute rule. Under certain conditions the epithelial cells may also form a cellular exudate. This does not include the assumption of a phagocytic activity of the alveolar epithelium, and it must be stated that tubercle bacilli, coal-dust, or degenerated cells are never found in the cells with the anisotropic lipoids.

Among the changes found, besides the specific tuberculous lesions, a diffuse fatty degeneration of the Kupffer cells of the liver is interesting. The Kupffer cells were crowded with fat droplets filling the protoplasm about the nuclei and the branches. The fat proved to be neutral fat. No anisotropic material was found in any part of the liver. The liver cells only occasionally contained a few medium-sized fat droplets.

In some of the reticular cells of the spleen a pale yellowish-brown lipoid pigment was present. The pulp showed myeloid metaplasia with a large amount of pseudo-eosinophilic myelocytes and single bone-marrow giant cells. No fat was seen in the kidneys.

V. Tuberculosis-Cottonseed-Oil Controls

The anatomical and histological pictures of the tuberculous changes of these rabbits differed in no way from those of the untreated controls. There was the same accumulation of isotropic fat about the caseous centres of the larger tubercles. The epithelioid cells of the young tuber-

cles and those in the periphery of the older tubercles were free from fat. Only in the tubercles of the suprarenal cortex did the cells contain more neutral fat than in the control.

VI. Tuberculosis-Cholesterol-Cottonseed-Oil Group

The tuberculous infection had not affected the cellular changes which characterized the cholesterol disease of the rabbit. Deposits of anisotropic lipoids were found in the same tissues and to the same extent as described in group I. Nor did the accumulation of the lipoids markedly influence the development of the tubercles. The gross findings were about the same as in the control rabbits. In the lungs there were grayish nodules, varying in diameter from 1 to 5 mm., the larger ones having yellow centres. The lymph nodes about the trachea were enlarged and firm, and showed on the cut-surface yellowish-white patches. The size of the spleen was about double the normal, but no gross lesions were noted in this organ. The liver contained numerous small yellow nodules. The adrenals were distinctly enlarged, and translucent nodules just visible to the naked eye were present in the broad yellowish-white cortex. The kidneys were free from tubercles, but were the seats of peculiar areas of cholesterol infiltrations mentioned in the description of the cholesterol-control rabbits.

The microscopic examination revealed that a large amount of double refracting fat had accumulated in the cells of the tubercles. The earliest stages of the tubercles already differed by their fat-content from the typical tuberculous lesions. In the lymph-follicles of the spleen and in the lymph nodes the reticular cells were frequently found swollen and deprived of their branches. They formed small groups of from 10 to 30 cells. Their nuclei were round or oval, sometimes kidney or sickle-shaped, with a granular arrangement of the chromatin. The protoplasm appeared lighter than in the typical epithelioid cells, and was filled with small fat droplets, which gave distinct double refraction. The droplets stained yellow with sudan III, and pale violet with nile-blue-sulphate. They were evenly distributed in the cytoplasm of the smaller cells, and in the larger cells showed a tendency to accumulate near the periphery.

Intracapillary syncytia and isolated giant cells were the first specific changes in the liver. They were observed in all the tuberculous animals, even if typical tubercles had not yet developed. These cells never contained fat in the control rabbits. However, in the rabbits that had

received cholesterol-oil double refracting droplets and granules were found in both the syncytia and the giant cells. The droplets in the giant cells occupied the periphery of the cells, between and inside the nuclei, thus leaving the centres free, in which occasionally one or two tubercle bacilli could be detected.

The miliary tubercle, in whatever organ it was located, appeared under the polariscope as a nodule of glistening crystals and granules. By heating to 80°C., and quickly cooling on the stage of the freezing microtome, the crystals were transformed into brilliant droplets, with a dark cross in the centre, thereby proving their chemical nature as cholesterol esters. In the sections stained with sudan III, all the epithelioid cells were full of yellow droplets. Nile-blue-sulphate stained them pale reddish violet. Reddish droplets were only occasionally found in the centre.

The tubercles in the cortex of the adrenals could hardly be distinguished under the polariscope from the surrounding tissue, because they contained almost as much anisotropic fat as the cortical cells (figs. 6, 7, 8). When, for comparison, sections of the adrenals of the tuberculosis-control rabbits were examined between crossed Nicols, the tubercles appeared as black holes in the glittering band of the cortex (figs. 3, 4).

In the description of the tuberculous lesions of the lungs of the control animals, it was mentioned that, although the tubercles were free from cholesterol esters, anisotropic fat droplets were observed in a cellular exudation in their surroundings. This difference could not be noted in the rabbits fed with cholesterol, because both the tubercles and the peritubercular areas were full of double refracting lipoids.

Also, in the larger tubercles with central caseation, the majority of the epithelioid cells contained anisotropic fat. The latter formed small and regular droplets, which either filled the whole protoplasm or were located in the periphery. Single cells free from fat were found in the mesial zone of the tubercles. Toward the centre the fat droplets became more irregular, and free fat was seen between the cells.

Nile-blue-sulphate stained most of the lipoid droplets, found in the epithelioid cells, pale reddish-violet. In the mesial parts droplets of pink or red-violet color were present, and near the necrotic centre the pink color predominated. Droplets only stained pink were visible in the necrosis itself.

According to the staining quality with Nile-blue-sulphate, we should expect to find but little anisotropic fat in the area of fatty degeneration

that surrounds the caseous centre. The latter may even be free from it. The examination of double refraction supports the result of the microchemical reaction of the Nile-blue-sulphate.

Only a few small double refracting crystals can be noted in the neighborhood of the caseation. In the centre itself optically active fat is often absent (figs. 1 and 2).

The disappearance of the double refracting fat in the necrotic tissue may be the result of its disintegration or of its transformation into an invisible form. It is possible that the anisotropic cholesterol esters are split up, and that the fatty acid became involved in the process of isotropic fatty metamorphosis, thus setting free the cholesterol. However, no increase of the characteristic crystals of free cholesterol can be noted in the necrotic masses, if compared to the controls.

A definite decision as to the fate of the cholesterol esters in the tubercles would only be possible by a chemical analysis. But the tubercles of the rabbit are too small to permit the exact separation of the different zones, which is necessary for such an analysis.

The large amount of cholesterol esters in the tubercles of the lung is of special interest because the lung tissue in experimental hypercholesterinaemia contains but little double refracting fat. From what preëxisting cells of the lung does the tubercle develop? Foot (64) regards the capillary endothelial cells of the lungs, like all other organs, as the only maternal cells of the epithelioid cells. But the endothelial cells of the capillaries of the lung do not take part in the anisotropic fatty infiltration. Does then the endothelial cell, transforming itself into an epithelioid cell, acquire a new quality? Or are the conditions for the deposition of the lipoid more favorable in the tubercle than they are in the capillaries? Or, finally, does not another type of cell participate in the building up of the tubercle? We think that the last possibility is the most probable one, if we remember that the adventitial cells of the smallest blood-vessels belong to the reticulo-endothelial cells, and that they are the only cells found in the lung of the cholesterol controls filled with cholesterol esters.

VII. Tuberculosis-Egg-Yolk Group

The infiltration of the tubercles with cholesterol esters was also evident from the experiments of feeding egg-yolk to tuberculous rabbits. But as in the controls the amount of double-refracting fat deposited in

the reticulo-endothelial cells was small, the changes in the tuberculous animals were much less pronounced than after feeding pure cholesterol dissolved in oil. It was also found by chemical examination of the blood that the egg-yolk in the tuberculous rabbits produced a less significant rise of the blood-cholesterol.

DISCUSSION

In discussing the results of our experiments, the fact should first be emphasized that the feeding of a large amount of oil, of cholesterol and oil, and of egg-yolk does not render the animals more resistant to tuberculosis. In spite of gaining weight and of an increase in the fat deposits, the animals that had received the lipoids did develop a pronounced tuberculosis.

The value of diets rich in fat in the treatment of tuberculosis has often been discussed. Lydia DeWitt (65), in her recent review of chemotherapy of tuberculosis, notes the statement of Weigert that overfeeding swine with fat increases their resistance to tuberculosis. According to Voigt, children nourished with fat show a greater immunity to tuberculosis. Pfenniger (66) found the life of tuberculous guinea pigs prolonged by feeding them with dog-fat.

A number of investigators, (Carrier (67), Metalnikow (68), etc.), believe that the supplying of large quantities of fat increases the lipolytic action of the blood that is often found to be low in tuberculosis (Bauer (69), Grineff (70)). The lipase is said to play a very important rôle in the destruction of the tubercle bacilli (Bergel, Metalnikow). Pirnatschewsky (71) tried to increase the lipolytic power of the diseased organism by a diet containing much fat and oil. He noted an improvement in the general condition of the patients following a restoration of the lipolytic titre of the serum. Cholesterol, however, does not markedly influence the serum lipase (Schoenheimer).

Calmette (72), who used lecithin and other lipoids to diminish the susceptibility of animals to tuberculosis, obtained negative results, though the lipolytic power of the serum went up during the time of the treatment. Gruber (73) found subcutaneous injections of the lipoids of the suprarenal cortex of no value for tuberculous guinea pigs. Droege (74) examined the chemical composition of the bodies of tuberculous guinea pigs, and saw no relation between the fat-content and the extent of the tuberculous infection. He does not believe overfeeding protects against tuberculosis.

It seems that the rôle played by cholesterol in infectious diseases has been overestimated. Of course the cholesterol metabolism of the animals studied (guinea pig, rabbit) differs from that of human beings. Thus, infections have no influence upon the cholesterol-content of the suprarenals of the rabbit. But the decrease of the cholesterol of the blood and of the cortex of the adrenal, which occurs in man during severe infections, does not necessarily indicate this lipoid to be used in the defensive reactions of the body. The diminished cholesterol-content of the blood rather is merely the symptom of a disturbed metabolism. And the disappearance of the cholesterol from the cells of the suprarenal cortex may result from a toxic injury to these cells affecting their functions (one of them being the piling up of cholesterol), just as the cells of other organs may lose their functions when under the influence of a noxious agent. There probably exists a difference between human beings and herbiverous animals as to the resistance of their suprarenal cells.

The tuberculous lesions in experimental hypercholesterinaemia participate in the accumulation of the cholesterol compounds. It is important to decide whether these changes are due to an active cellular process, or whether they merely represent a form of degeneration uncommon in typical tuberculosis.

It has already been said that the cells of the tubercles originate in the reticulo-endothelial cells, which in hypercholesterinaemia contain a large amount of cholesterol esters. Chalatoff distinguishes between the cholesterol deposits of the epithelial cells and those of the mesenchymatous cells. Preceding regressive changes of the epithelial cells are necessary to allow the cholesterol esters to enter the protoplasm. In the liver cells isotropic fat droplets appear before double refracting crystals are visible (Chalatoff). Biach and Weltmann produced an anisotropic fatty infiltration of the renal epithelium of rabbits which received cholesterol and uranium nitrate. The latter caused a severe degeneration of the epithelium of the *tubuli contorti*. Borst (75) found much double refracting fat in an ovary which had been transplanted under the skin of a rabbit fed with cholesterol.

In the mesenchymatous cells, however, anisotropic fatty infiltration does not depend on diminished vitality. There are apparently in these cells preëxisting structures with an affinity for the lipoid. Therefore these cells are otherwise not markedly affected. They may still be accessible to vital stains, which are sensitive reagents as to the integrity of these cells, though the intensity of the staining may be more or less

reduced. Intact cells either take up the vital stain as granules, or they do not stain. Degenerated cells stain diffusely. By combining the cholesterol feeding with the injections of vital stains, the reticulo-endothelial cells are full of lipoid droplets between which single granules of the stain may be found (Chalatoff).

The cells laden with anisotropic fat share in the formation of inflammatory exudations like normal histiocytes. (Anitschkow (76), Kon and Yamada (77), Borst.) They are able to proliferate, to form tubercles and to phagocytose tubercle bacilli. The tubercle bacilli do not actively invade the lipoid cells, because they are often found granularly degenerated in these cells. The anisotropic fat disappears in the degenerated and necrotic parts of the tubercles.

These observations indicate that the storage of double refracting cholesterol esters in the tubercles is an active cellular process.

There is some resemblance between the anisotropic fatty infiltration of the histiocytes and the vital staining. The accumulation of the fat in the living tuberculous tissue, however, is much more pronounced than any kind of vital stain, apart from india-ink. The explanation is as follows: The vital stains are colloidal solutions which surround the different cells only for a short time, because they are soon excreted. The cholesterol accumulates in the blood-stream, thus securing a continuous contact with the cells.

CONCLUSIONS

1. The epithelioid cells of the tubercles in experimental hypercholesterinaemia are filled with double refracting cholesterol compounds like the reticulo-endothelial cells from which they are derived. The accumulation of the lipoid is limited to the living tuberculous tissue. With the onset of degeneration the anisotropic fat disappears, to be replaced by isotropic fat giving the microchemical reactions of neutral fat. In the necrosis only a few double refracting crystals are found.

2. The tuberculous cells, in spite of the lipoid droplets in their protoplasm, phagocytose and destroy tubercle bacilli. Therefore these cells cannot be called degenerated cells.

3. The histiocyte, transformed into the epithelioid cell, retains some of the functions of the original cell. It is still able to take up cholesterol esters as fluid crystals when the surrounding tissue fluid contains an excessive amount of this lipoid.

4. The oversaturation of the body of the rabbit with cholesterol does not protect the animal against tuberculosis.

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FIG. 1. TUBERCLE WITH CENTRAL CASEATION AND BEGINNING CALCIFICATION OF THE LUNG

Rabbit fed with cholesterol-cottonseed oil. Frozen section, hematoxylin, mounted in glycerol-gelatin. × 100.

FIG. 2. SAME SECTION BETWEEN THE CROSSED NICOLS OF A POLARISCOPE

Note the dark centre, corresponding to the caseous area in fig. 1, and the large amount of double refracting crystals in the living tuberculous tissue. × 80.

FIG. 3. TWO MILIARY TUBERCLES IN THE CORTEX OF THE ADRENAL OF A CONTROL RABBIT

(Technique as in fig. 1.) × 60

FIG. 4. SAME SECTION BETWEEN CROSSED NICOLS

The tubercles are free from fat and appear as black holes. × 60

FIG. 5. MILIARY TUBERCLE IN THE CORTEX OF THE ADRENAL OF A CONTROL RABBIT

(Paraffine section, hemalaun, eosin.) × 230. The epithelioid cells are distinctly demarcated from the surrounding cortical cells.

FIG. 6. MILIARY TUBERCLE IN THE CORTEX OF THE ADRENAL OF A RABBIT, FED WITH CHOLESTEROL-COTTONSEED OIL

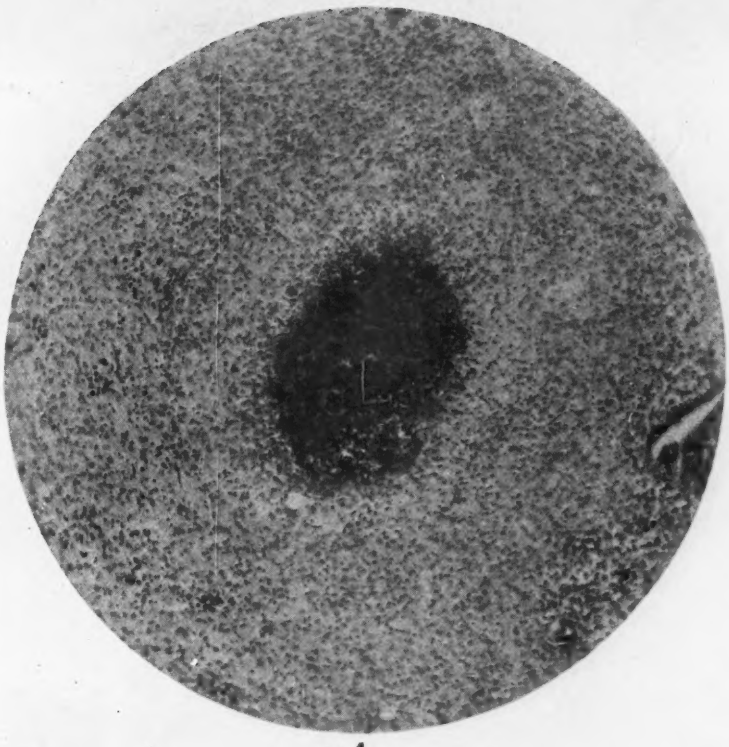
(Technique as in fig. 1.) × 60

FIG. 7. SAME SECTION BETWEEN CROSSED NICOLS

The tubercle can hardly be distinguished from the surrounding cortical cells, because it is full of double-refracting crystals. × 60

FIG. 8. MILIARY TUBERCLE IN THE CORTEX OF THE ADRENAL OF A RABBIT, FED WITH CHOLESTEROL-COTTONSEED OIL

(Technique as in fig. 5.) × 230. The foamy, lipoid-containing cells of the tubercle resemble the cortical cells.



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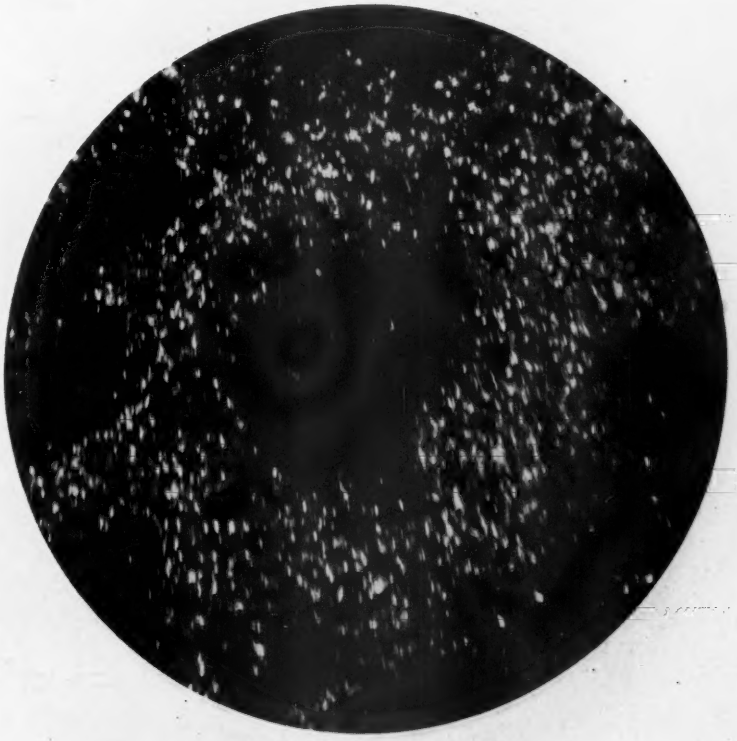

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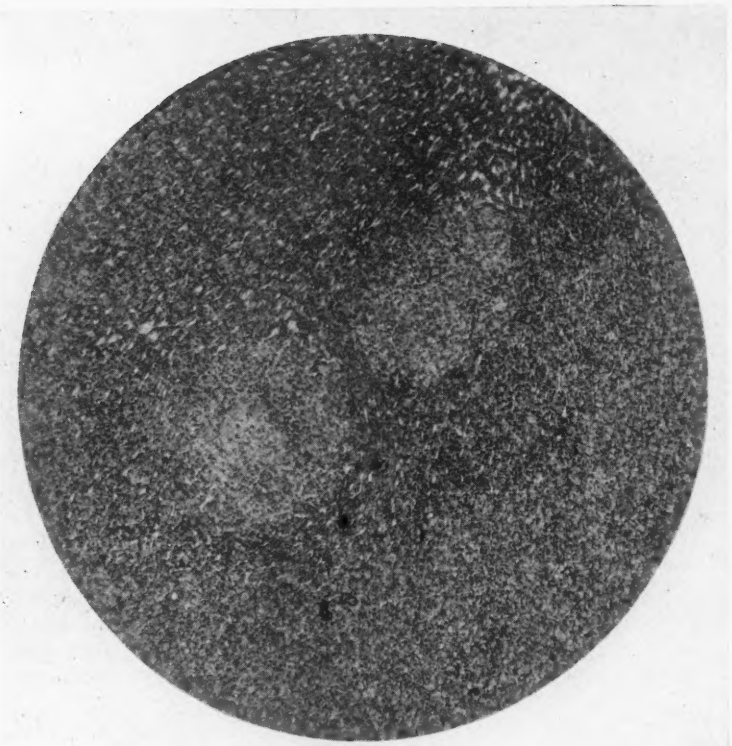

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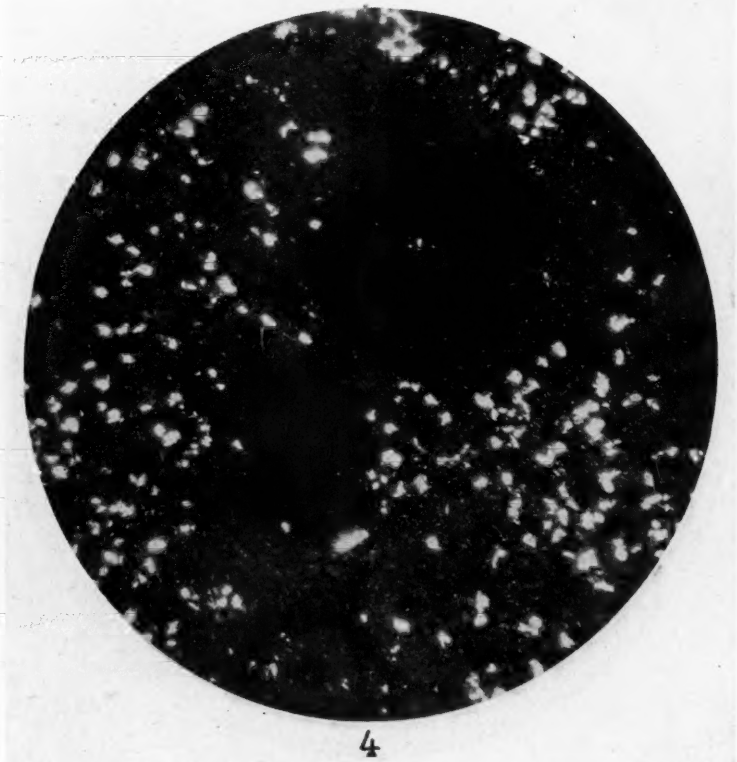

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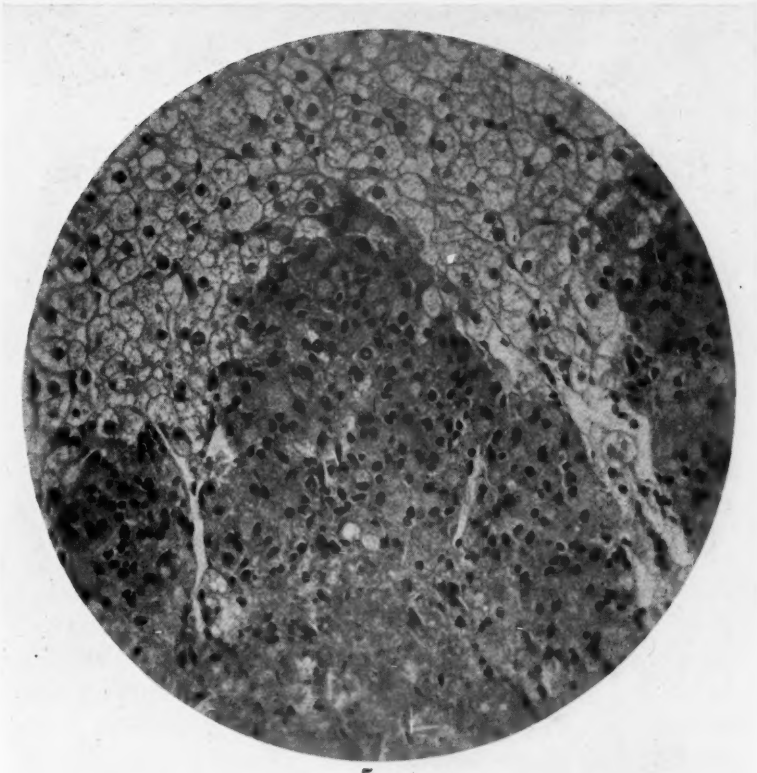

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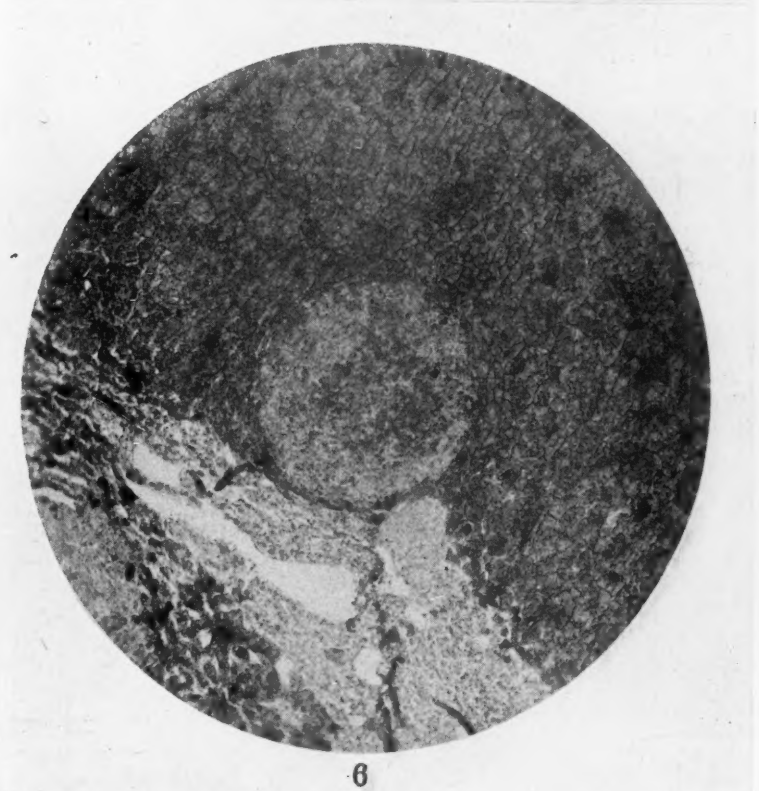

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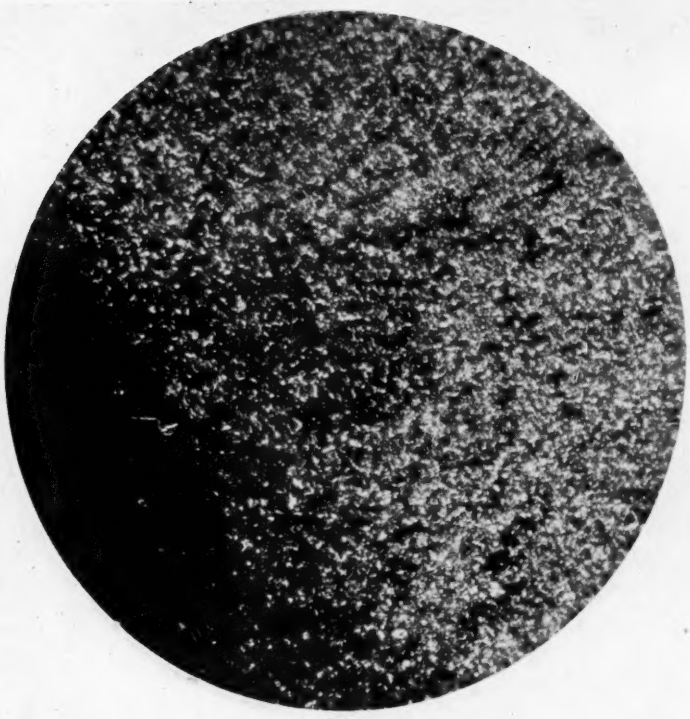

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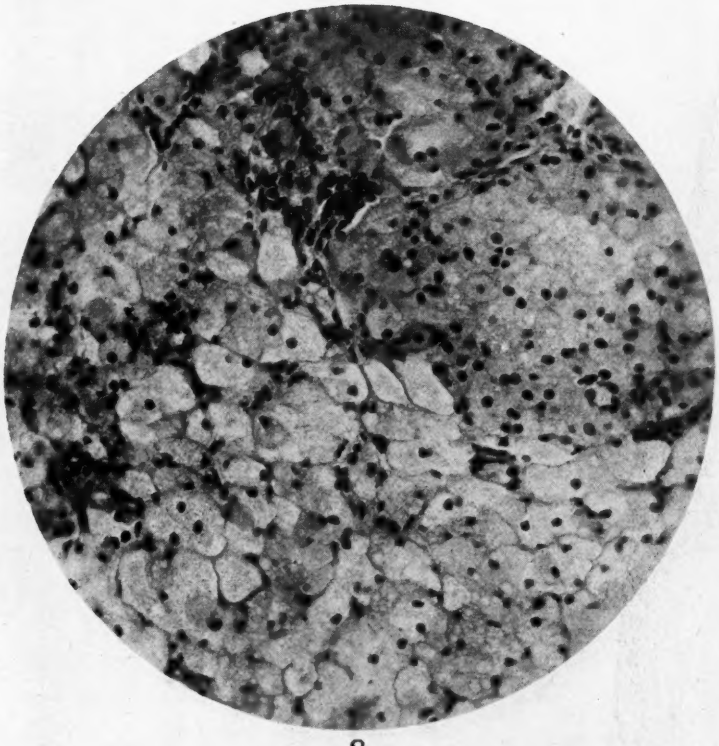

8

EXPERIMENTAL TUBERCULOSIS IN RATS ON VARIED DIETS [1]

FAT AND VITAMINE FACTORS

LINDA B. LANGE

In an earlier communication (1) the tissue-reaction of rats to infection with the bovine tubercle bacillus and the effect on the character of the reaction of variation in the protein and salt factors in the diet were reported. The present paper deals with the effect of the variation in the diet of fats and the so called vitamines as it affects the response to tubercle-bacillus infection.

The general plan of the experiment was the same as in the earlier series. Grown albino rats from the open market, assembled from various dealers, were used instead of the hooded rats bred in the Department of Chemical Hygiene. While it was thought that variation in hereditary factors so introduced might perhaps affect the results, this has not been apparent. The sexes were segregated and the animals kept on the routine diet for four weeks, and then placed on the experimental diets for a month. At the end of this time they were infected subcutaneously in the right groin with a suspension of the Saranac strain, *B1*, of bovine tubercle bacillus. The emulsion was not standardized by counting as before. It seemed from earlier observations to be sufficiently exact, in view of the high resistance of the rat, to prepare a heavy suspension with the ordinary precautions against the inclusion of large bacillary clumps, and to inject this preparation in quantities of 0.1 cc. per 100 gm. body weight. The course of the infection was followed at intervals by gross and histological examinations of the tissues, including a search for bacteria stained by the Ziehl-Neelsen method for acid-fasts and the MacCallum combined Goodpasture and Gram-Weigert stain for Gram-negative and Gram-positive bacteria. For each experimental diet 18 rats were infected and 6 kept as uninfected controls. For the adequate control diet 12 were infected. Uninfected controls on adequate diet

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were omitted, because such a group from the earlier experiment supplied the necessary information regarding this type of material. At each of the first five weekly examinations, there were killed with ether 3 infected and one uninfected animal from each experimental diet group, and 2 from the infected group on the adequate control diet. The sixth and last lot were allowed to live beyond the first five weeks after infection and were examined as they happened to die, the last survivors being killed at seventeen and one-half weeks. The weights were recorded just before infection and at the time of autopsy.

TABLE 1

	I	II	III	IV	V
	Low fat-soluble vitamine	Low water-soluble vitamine	Fats I	Fats II	Adequate control diet
Rolled oats, raw	40		40	40	40
Rolled oats, prepared		83.5			
Gelatine	5	5			5
Casein, raw					5
Casein, prepared	5	5			
NaCl	1		1	1	1
$CaCO_3$	1.5	1.5	1.5	1.5	1.5
Wesson Oil			15	5	
	(once a week)				
Butter fat	2	5	2	10	3
Codliver oil				2	
		(once a week)			
Wheat germ		2			
Dextrin	47.5		40.5	40.5	44.5

The experimental diets were planned to test the effect of the following variations: first, deficiency in fat-soluble vitamine; second, deficiency in water-soluble vitamine; third, a high fat-content combined with low protein and deficiency in fat-soluble vitamine; and fourth, a high fat-content combined with a low protein-content but with no vitamine deficiency. No study of the antiscorbutic vitamine was attempted. The diets were made up according to table 1.

The ingredients were prepared according to the McCollum methods. The "prepared" rolled oats and the "prepared" casein were free of vitamines. In the second diet, the necessary sodium chloride was present in the "prepared" rolled oats. I am indebted to the Lilly Research Laboratories for the codliver oil and to the Washburn-Crosby Company for the wheat germ. All the solid constituents were finely ground, in

order to ensure a homogeneous mixture and one which could not be separated by the animals. They had free access to the dry food and to drinking fountains kept filled with fresh tap-water.

Since the time that this feeding experiment was done (in the early part of 1923) attention has been drawn by Huldschinsky, Steenbock, Hess and others to the relation of light and nutrition. It should, therefore, be recorded that the food mixtures in this case were made up and stored in mason jars of greenish glass, several jars of each diet at a time. One jar, at a time, of each mixture was taken to the animal room and kept on a windowsill, where direct sunlight shone for part of each clear day. At all times, however, the light passed through the heavy glass of the windowpane as well as through that of the jar.

The tissue-reaction to infection in all the rats proved to be essentially the same as that previously described and illustrated (1) for rats on a normal maintenance diet. The amount of tuberculous tissue was greater in all the animals of this series than in those of the first, probably because of the somewhat heavier infecting dose. One week after infection epithelioid proliferation was present in the subcutaneous tissue at the site of inoculation and in the inguinal and iliac lymph nodes of the infected side. It showed already a tendency to pass from the early diffuse to the subsequent sharply demarcated arrangement, the latter of which was almost constantly present in the two-week lesions. From the second to the fourth week, but most commonly at the third, regression of the epithelioid tubercles began, as evidenced by one or more of the following signs: a decrease in the number or in the intensity of staining of the nuclei of the epithelioid cells; a yellowish pigmentation of the whole epithelioid tubercle; a slight invasion by surrounding lymphocytes breaking the otherwise sharp contour of the tubercle. These were followed by progressive shrinkage and disintegration. There was no difference, however, between the five groups in this series, none of the experimental diets causing any variation from the reaction obtained on the control diet. Tubercle bacilli were easily found in large numbers in all the early lesions, and decreased in numbers during the course of the infection. Again, the demonstration of the tubercle bacillus was far more successful by the Gram-Weigert than by the Ziehl-Neelsen stain. Of the 84 infected rats of this experiment, there are complete data on this point for 61 animals. Of these there were 11 in which neither stain revealed the bacteria; one in which one acid-fast bacillus was found, but none by the gram stain; one in which there were few Gram-positive

but somewhat more numerous acid-fast bacilli; one in which the subcutaneous tissue showed more by the Gram than by the Ziehl-Neelsen stain, but the inguinal lymph node showed a few acid-fast but no gram-positive bacilli. In the remaining 47, in which bacilli were found by both stains, they were far more numerous and more easily detected by the Gram-Weigert method. In several instances in this group they were almost missed, or only one bacillus or a very few bacilli were found by the acid-fast stain, while the Gram stain revealed them to be present in considerable numbers. The possibility of secondary invaders can be excluded.

As the disintegration and absorption of the tuberculous tissue proceeded, the bacilli became fewer. This was approximately the same in all the diet groups, but in one group (*Fats I*) no bacilli were found in the last survivors killed at seventeen and a half weeks, though remnants of tubercles could still be discovered. Rats from the control group and those on low water-soluble vitamine and on *Fats II* still showed bacilli at this time. The animals on low fat-soluble vitamine had all died within eight weeks, with bacilli still demonstrable.

Tuberculous lesions outside of the regional lymph nodes were practically absent. Two rats on different diets killed at three weeks after infection showed a few tubercles in the lymphoid tissue of the spleen, in which no acid-fast bacilli but a few granular Gram-positive rods were found. One rat on the low water-soluble vitamine diet had tubercles in the left inguinal lymph node as well as on the right side, two weeks after the customary inoculation in the right groin. The spleens, except for the few tubercles noted in two cases, the livers, kidneys, tracheal lymph nodes and lungs showed no changes that could be correlated with the infection or the diets.

The weights, recorded at the beginning and end of the period of infection, showed nothing significant. While there was perhaps a somewhat more marked downward trend in the rats on deficient diets,—especially in those on low water-soluble vitamine,—as compared with the normal group, there was no clear-cut difference in any given diet-group between the infected and uninfected animals.

As usual, many of the rats were afflicted with the common mucopurulent bronchitis and bronchiectasis. This did not appear to affect the results of the experiment, nor was it clear that any one of the dietary deficiencies here tested affected the incidence or extent of this complicating infection. The number of animals is probably too small to

make these results significant, but it is interesting that they should not be in accord with the current idea that fat-soluble vitamine protects against infection and that lack of vitamines predisposes to infection.

The only effect, then, which may be ascribed to the diets used in this series would seem to be the earlier complete disappearance of tubercle bacilli, as shown in the animals on *Fats I* (high fat, low protein, low fat-soluble vitamine).

While there is a general impression that foods rich in vitamines, and therefore the vitamines themselves, are advantageous in combating tuberculosis, the recorded experimental work on this point is meagre. Gloyne and Page (2), testing vitamine-A deficiency in young white rats, found no effect on the course of the tuberculous infection. Smith (3), working with guinea pigs, came to no very definite conclusions as to the protective power of fat-soluble A. Davis (4), using young growing guinea pigs, thought that the addition of skimmed milk to a deficient diet protected the animals against tuberculosis to some extent, but her records are too indefinite to evaluate. Finally, Bassett-Smith and Gloyne (5), in a small series of tuberculous guinea pigs, did not find that excess of vitamine-B in addition to an adequate diet influenced the course of the infection.

Two difficulties attending work of this kind are the dietary management of guinea pigs, which are susceptible to tuberculosis, and the high resistance to tuberculous infection of rats which are suitable for feeding experiments.

SUMMARY

1. Grown albino rats, on diets calculated to test the effect of fats and vitamines, were inoculated with heavy doses of bovine tubercle bacilli, and the course of the infection was followed, as evidenced by the tissue-reaction, the presence of tubercle bacilli and the change in weight. The course was essentially the same in the control and test-diet groups with the single exception of the group on a diet high in fat but deficient in vitamines, which showed an earlier complete elimination of the tubercle bacilli.

2. Previous observations regarding the staining properties of tubercle bacilli in rat tissues were confirmed, in that it was found that they were stained by the Gram-Weigert stain in more cases than by the Ziehl-Neelsen, and that when they were demonstrable in the same case by both methods, the Gram stain revealed them in far greater numbers.

It is a pleasure to acknowledge my indebtedness to Dr. E. V. McCollum for suggestions regarding the dietary aspects of this investigation.

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A NOTE ON THE VIRULENCE OF THE SARANAC LABORATORY R1 STRAIN OF TUBERCLE BACILLI[1]

GERALD B. WEBB, CHARLES T. RYDER AND CHARLES H. BOISSEVAIN

Because of their bearing on the subject of protective inoculation with live attenuated cultures of tubercle bacilli, a subject which Calmette's communications (1), (2), (3) have brought forward anew, we are reporting a very small group of observations on the virulence of the Saranac *R1* strain. Our experiments do little more than confirm observations of Baldwin and Gardner (4) to the effect that this strain, though usually of very low virulence, sometimes causes chronic progressive general tuberculosis, which may prove fatal.

On July 31, 1922, guinea pig *R1K1* was inoculated in the right groin with a heavy suspension of an original culture of R1 which had been sent us through the courtesy of Dr. Krause. The culture was contaminated in making transplants and was therefore put into a guinea pig. The animal developed to all appearances the typical R1 disease as described by Krause (5). There was a nodule but no ulcer at the point of inoculation, and enlargement of the right inguinal nodes, which slowly increased and then diminished in size, the animal remaining in apparently good health for more than a year, then becoming thin and sick, and dying 15 months after inoculation. At autopsy it showed very extensive generalized tuberculosis with both fibrosis and caseation.

Of 3 guinea pigs (*R1K2, 3,* and *4*), inoculated by subcutaneous implanation of tissues from *R1K1,* two died three and a half months later, immediately following the injection of an extremely toxic tuberculin, previous to which one was thin and sick, while the other seemed well; both showed advanced generalized tuberculosis. The third (*R1K4*) developed an ulcer *which healed,* lived 7 months and died with paralysis, atrophy, and sloughing of the hind-quarters, which we have observed in other guinea pigs with chronic tuberculosis. At autopsy it showed tuberculosis of the inguinal lymph nodes only.

[1] From the laboratories of the Colorado Foundation for Research in Tuberculosis, Colorado Springs, Colorado.

Two guinea pigs (*R1K5* and *6*) were inoculated in the groin with a heavy suspension of a culture recovered from *R1K2*. One died in two and a half months, and showed generalized tuberculosis with extensive involvement of the peritoneum, indicating that the inoculating needle had been forced through into the peritoneal cavity. The other had an ulcer *which healed*, and lived nearly six months. At autopsy it showed generalized tuberculosis. A control inoculated with a stock laboratory culture died in three months and showed very extensive generalized tuberculosis.

In interpreting these results we have to consider the possibility of an accidental virulent infection in guinea pig *R1K1*. However, the chronic course of the disease as compared with that produced by ordinary strains, and the ulceration followed by healing, in *R1K4* and *R1K5*, make this very improbable. We are undertaking a larger and more fully controlled series of inoculations with the R1 strain, the strains recovered from *R1K2* and *3*, a strain of diminished virulence recovered from a case of chronic tuberculosis produced in a guinea pig by implanation of incubated tuberculous tissue (6), an old laboratory strain, and a strain recently cultivated from sputum.

In 1919 Krause (5), in discussing the R1 strain, wrote, "If inoculated only once, even in relatively large dosage, it never brought about the death of the animal." Rarely slight visceral lesions were found in animals which had gone through pregnancies, but otherwise "the animals invariably kept in perfect physical condition, and when killed after two years or more showed no gross visceral lesions and but slightly altered regional lymphatic nodes."

In 1921 Baldwin and Gardner (4) published the report of a very extensive series of experiments on reinfection in tuberculosis, in which much use was made of the R1 strain. In the course of these experiments they infected many guinea pigs with R1 tubercle bacilli by inhalation. Of one such group they record, "Many of these animals died, and in five instances among 40 guinea pigs the disease had spread to the spleen and liver." They note that these were young animals. They also inoculated 18 guinea pigs subcutaneously with R1 emulsion and with tissues from animals previously infected with R1. Several animals in each group developed a chronic generalized tuberculosis like that which occurred in our guinea pig *R1K1*, and one in each group apparently died of it about a year after inoculation. In their experiments the possibility of accidental virulent infection was virtually excluded.

Very recently Rosenberger (7) has reported the production of large caseous abdominal masses, with smaller disseminated nodules, by intraperitoneal inoculation of guinea pigs with an R1 strain which he had kept under cultivation since receiving it in 1904. In one instance the animal died, apparently of this infection, after about two years.

CONCLUSIONS

1. A strain of tubercle bacilli which has appeared to be of constantly low virulence may in some cases cause progressive fatal tuberculosis.
2. The bacilli recovered from such cases may be more virulent than the original strain, though less so than average strains.
3. The bearing of these facts on any method of vaccination which employs living attenuated bacilli is obvious.

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STUDIES ON THE CALCIUM CONTENT OF BLOOD OF NORMAL AND TUBERCULOUS SUBJECTS[1]

PHILIP B. MATZ[2]

1. CALCIUM CONTENT OF NORMAL HUMAN SERUM

Calcium is of vital importance to the body because of the part it plays in the coagulation of blood, the irritability of the heart, the excitability of the central nervous system, and the formation of bone. It has been shown that most of the calcium of the blood is found in the serum or plasma and that the blood corpuscles are low in this element. Any change of the calcium concentration of the blood in health or disease is possible of detection, therefore, by estimation of the calcium content of the serum or plasma.

TABLE 1

Calcium content of normal human blood found by various observers

	MILLIGRAMS PER 100 CC.
Jansen	12.46
Dennstedt and Rumpf	11.6
Hawk	10
Myers	10
Salvesen and Linder	10
Howland and Kramer	10
Denis and Hobson	10

The calcium of the blood of infants is low for several months after birth and gradually increases until it is almost double that at birth, and then there is a gradual decrease.

Calcium is found in the blood to the point of saturation. It is held in solution by the colloids and carbon dioxide, being present as calcium bicarbonate and dicalcium phosphate. These are precipitated when the carbon dioxide of the blood is reduced.

It was thought advisable to begin the calcium studies by a series of blood-calcium estimations on healthy subjects, for the purpose of

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TABLE 2

Calcium of serum in normal subjects

CASE NUMBER	NAME	AGE	CALCIUM MGM. IN 100 CC. SERUM
1	L. T.	30	10.0
2	W. D.	24	11.1
3	W. P.	23	10.0
4	O. W.	42	9.8
5	A. E. D.	20	12.0
6	L. D.	23	11.6
7	C. P. C.	22	10.3
8	O. J.	23	10.8
9	L. D.	24	10.8
10	C. H. D.	39	9.8
11	A. B. S.	25	9.0
12	W. S.	28	9.1
13	A. Z.	36	9.1
14	T. A.	30	9.3
15	J. B.	16	11.6
16	V. W.	22	9.1
17	W. F. B.	24	10.0
18	F. B.	25	9.5
19	W. M.	51	10.0
20	G. S.	28	10.4
21	W. P.	22	10.5
22	O. W.	22	10.4
23	N. E.	22	10.3
24	C. C.	23	10.9
25	G. D.	38	10.0
26	C. M.	29	9.2
27	A. M.	22	10.5
28	J. F. A.	21	10.4
29	O. R.	25	11.0
30	G. C.	34	9.4
31	C. H.	34	10.4
32	E. H. F.	24	11.0
33	A. J.	20	10.0
34	C. S.	18	11.3
35	A. A. W.	19	11.0
36	C. H. P.	22	9.2
37	R. H.	21	10.8
38	R. H. C.	23	9.8
39	A. R. M.	18	10.3
40	E. C. P.	21	9.6
41	E. C. P.	19	10.0
42	C. H. P.	22	10.0
43	C. L.	19	10.3
44	M. J.	21	11.7
45	P. T.	24	9.5
46	B. N.	26	10.4
47	R. E.	19	10.6
48	W. C.	43	11.0
49	B. F.	21	10.3
50	F. O.	21	11.3

obtaining normal values. The technique used was that of Kramer and Tisdall. The specimens of blood were obtained in the morning on a fasting stomach, the subjects having been previously instructed not to ingest food or water before specimens were obtained. The findings (table 2) were used as criteria in the calcium studies which followed. Most of the subjects were employees of U. S. Veterans' Hospital No. 93, whose ages ranged from 16 to 43. The calcium values were from 9 to 12 mgm. per 100 cc. serum, with an average of 10.28 mgm.

2. CALCIUM OF THE BLOOD SERUM IN PULMONARY TUBERCULOSIS

A great many observers maintain that tuberculosis is accompanied by a demineralization, particularly of calcium. Croftan is of the opinion that this reduction is due to the binding of calcium by toxic products, resulting from tuberculous infection. Sweany, Weathers and McCluskey found that pulmonary tuberculosis with hemorrhages is accompanied by a reduced calcium content of the blood, while other cases of pulmonary tuberculosis showed very little variation in the calcium content from normal.

On the other hand many observers are firmly convinced that there is no reduction of calcium in tuberculosis. Halverson, Mohler and Bergeim in 1917 conducted a series of blood-calcium determinations on cases of pulmonary tuberculosis and found no marked variation from normal. Wells, as a result of experimental work on animals, concluded that there is no deficiency of calcium in the blood or tissues in tuberculosis.

It is thought that the work that has been done on this problem is not very convincing. A good deal of the experimental work having been done on animals, it is quite possible that the findings in human beings might not be the same. It was therefore decided to make a study of the calcium content of the human blood in tuberculosis at this hospital, where the work could be carefully controlled, where the patients could be placed on a proper dietetic regimen, and where the necessary precautions as to laboratory technique could be taken. The patients were in different stages of pulmonary tuberculosis, some of them with complications. (See table 3.)

In studying table 3 it is noted that there is very little variation in the blood-calcium findings in the different stages of pulmonary tuberculosis; even cases complicated by chronic parenchymatous nephritis show an

average concentration of 9.22 mgm., which is within normal limits. Incipient cases of pulmonary tuberculosis show an average concentration of 10.38 mgm. The highest calcium figures were obtained in apparently arrested cases of chronic pulmonary tuberculosis. This was to be expected, as it is in such cases that maximum calcification of lung tissue takes place. Attention is invited to the fact that cases of advanced pulmonary tuberculosis, both with and without hemorrhages, show the same blood-calcium concentration, namely, 9.25 mgm.

TABLE 3

Average calcium content of serum in the different stages of pulmonary tuberculosis

	MILLIGRAMS PER 100 CC.
Tuberculosis, chronic, pulmonary apparently arrested (6 cases)	10.78
Pulmonary tuberculosis, incipient (10 cases)	10.38
Chronic pulmonary tuberculosis with moderate amount of lung involvement, clinical activity not pronounced (20 cases)	10.0
Chronic pulmonary tuberculosis with tuberculosis of kidney (1 case)	9.7
Chronic pulmonary tuberculosis with small amount of lung involvement and with history of hemorrhages (2 cases)	9.4
Chronic pulmonary tuberculosis, advanced, with large amount of lung involvement and with history of hemorrhages (9 cases)	9.25
Chronic pulmonary tuberculosis, advanced, with large amount of lung involvement and with no history of hemorrhages (20 cases)	9.25
Chronic pulmonary tuberculosis with chronic parenchymatous nephritis (4 cases)	9.22

3. ABSORPTION AND UTILIZATION OF CALCIUM OF THE FOOD IN NORMAL SUBJECTS

Food being the source of the calcium of the body, it was thought important to make a study of the rate and manner in which the body absorbs and utilizes this element. Calcium in the food is usually in organic combination, as in milk, eggs, vegetables and cereals. There is also an intake of calcium in drinking water, which is an inorganic form.

As to the relative availability of these two forms, there is considerable difference of opinion. Givens found that 0.34 gm. CaO, in the form of dried skimmed milk, when added to a calcium-poor basal ration, would produce a positive calcium balance, while it took 1 gm. of calcium oxide in the form of lactate to accomplish the same end. Towles found that the addition of calcium lactate to a calcium-poor diet, which was giving a negative balance, resulted in a positive balance, which soon became

negative; while the addition of the same amount of calcium oxide, in the form of milk, gave a higher and a more lasting calcium-oxide retention.

The normal adult requirement of calcium per day has been variously estimated. Bunge puts it at 0.33 to 0.38 gm. calcium oxide; Bertram at 0.38 gm. calcium oxide; Renvall at 1.19 to 1.26 gm. calcium oxide; VonWendt at 0.8 gm. calcium oxide; Nelson and Williams at 0.95 to 1.43 gm. calcium oxide; Sherman at 0.9 to 1 gm. calcium oxide per day, and he further states that 1 gm. of calcium should accompany the ingestion of 100 gm. of protein. The consensus of opinion is that 1 gm. of calcium oxide for every 3,000 calories is the proper mineral requirement of the body.

In infancy and childhood the question of calcium metabolism is of paramount importance, because of the need of the body for this element in growth and in bone formation. Herbst maintains that children six to seven years of age require 0.3 to 0.5 gm. calcium oxide per day, and that children 14 years of age should ingest from 0.6 to 0.9 gm. for proper metabolism.

In young animals fed on a calcium-poor diet the bones may contain a normal percentage of calcium, but the new bone formed is thin, pliable, deformed and fragile. These animals, according to Weiser, are undersized, and have poor appetites and defective nutrition.

Clark, as well as Denis and Minot, maintain that the ingestion of a calcium-poor or calcium-rich diet seems not to affect the blood calcium. Voorhoeve claims to have found an increased blood calcium after the ingestion of food containing large amounts of calcium. The absorption of the calcium takes place in the intestinal tract, the blood utilizing the amount necessary for body economy, and the excess is excreted by the intestines and to a less extent by the kidneys. When calcium is present in large quantities in the blood of rabbits, calcification of dead tissue takes place very rapidly. If the blood vessels of the rabbit's kidney are ligated, the tissue becomes quite densely calcified within a few days.

It is thus seen that the literature on the absorption and utilization of calcium of the food in normal subjects is conflicting. The work reported herein was done for the purpose of observing the effect of calcium of the food on the blood-calcium concentration and to see whether there is a certain characteristic rate of absorption and utilization of this element by the blood.

TABLE 4

Subject W. D. March 20, 1924. Table of regular diet with calcium content of food showing effect after ingestion on blood-calcium concentration

REGULAR DIET	QUANTITY BY WEIGHT	CALCIUM OXIDE	CALCIUM	PROTEIN	CARBOHYDRATE	FAT	CALORIES
	gm.						
Cream of tomato soup	292	0.272	0.191	6.5	12.6	19.52	230.43
Broiled steak	105.60	0.0128	0.0099	17.07		25.74	300
Mashed potato	126.07	0.0548	0.0387	3.355	22.188	5.719	163.7
Buttered peas	96	0.0195	0.014	3.325	8.86	5.7	50
Grapefruit	212.08	0.0506	0.04	1.72	22.1	0.45	100
Bread	39	0.015	0.011	3.6	20.39	0.46	100
Butter	6.50	0.0015	0.001	0.065		5.52	50
Milk	288	0.486	0.348	9.52	14.44	11.56	200
Total in grams		0.9176	0.6536	45.155	100.578	74.669	1,194.13

TABLE 5

Case W. D. Protocol of blood-calcium percentage before and after the ingestion of above meal

HOUR	CALCIUM OF BLOOD
	mgm.
9:00 A.M.	10.9
9:45 A.M.	Ingestion of meal
10:45 A.M.	10.9
11:45 A.M.	9.9
12:45 P.M.	9.3

TABLE 6

W. D. March 25, 1924. Table of diet with excessive calcium content showing effect after ingestion on blood-calcium concentration

	CALCIUM OXIDE	CALCIUM	PROTEIN	CARBOHYDRATE	FAT	CALORIES
Cream of tomato soup	0.272	0.191	6.5	12.6	19.52	230.43
Puffed omelet	0.139	0.1	20.9		16.74	222
Creamed cauliflower	0.225	0.167	3.18	2.81	16.82	158.33
Spinach	0.098	0.07	2.19	0.31	3.35	25
Cottage cheese	0.297	0.212	19.04	3.92	0.91	100
Olives	0.057	0.041	0.37	9.23	3.88	100
Baked custard	0.289	0.207	25.63	7.22	11.03	208.67
Bread	0.015	0.011	3.6	20.39	0.46	100
Butter	0.0015	0.001	0.065		5.52	50
Buttermilk	0.41	0.294	8.38	13.42	1.4	100
Total in grams	1.8035	1.294	89.855	79.90	79.63	1,294.43

TABLE 7

Case W. D. Protocol of blood-calcium percentage before and after ingestion of above meal

HOUR	CALCIUM OF BLOOD
	mgm.
9:00 A.M.	9.7
10:30 A.M.	Ingestion of meal
11:30 A.M.	10.5
12:30 P.M.	10.7
1:30 P.M.	10.9
3:30 P.M.	10.4

TABLE 8

Diet for one day showing calcium content of food

	QUANTITY BY WEIGHT	CALCIUM OXIDE	CALCIUM	PROTEIN	CARBOHYDRATE	FAT	CALORIES
	gm.						
Breakfast:							
Grapefruit	212.08	0.056	0.04	1.72	22.1	0.45	100
Shredded wheat	27.4	0.011	0.016	3.51	20.59	0.49	100
Cream	102.8	0.144	0.1	2.56	2.31	19	200
Sugar	25				25		100
Eggs (2)	76.2	0.063	0.045	9.06		7.08	100
Bread	39	0.015	0.011	3.6	20.39	0.46	100
Butter	13	0.003	0.002	0.13		11.05	100
Coffee							
Total		0.292	0.214	20.585	90.39	38.53	800
Dinner:							
Cream of tomato soup	292	0.272	0.191	6.5	12.6	19.52	230.43
Pork chops	73.8	0.012	0.0093	16.1		15.06	200
Mashed potato	126.07	0.0548	0.0387	3.355	22.188	5.719	163.70
Spinach	104.6	0.098	0.07	2.19	0.31	3.35	25
Bread	39	0.015	0.011	3.6	20.39	0.46	100
Butter	6.5	0.0015	0.001	0.065		5.52	50
Baked custard		0.289	0.255	25.63	7.22	11.03	208.67
Milk	288	0.486	0.348	9.52	14.44	11.56	200
Total		1.2283	0.924	66.96	77.148	72.219	1,177.8
Supper:							
Broiled steak	105.6	0.0128	0.0099	17.07		25.74	300
Baked sweet potatoes	202.8	0.046	0.032	2.92	44.4	1.2	200
Creamed cauliflower	142.9	0.225	0.167	3.18	2.81	16.82	158.33
Sliced peaches	106.6	0.0265	0.019	0.745	11.515	0.105	50
Bread	39	0.015	0.011	3.6	20.39	0.46	100
Butter		0.0015	0.001	0.065		5.52	50
Milk	288	0.486	0.348	9.52	14.44	11.56	200
Total		0.8128	0.5879	37.11	93.555	61.405	1,058.33
Total for 3 meals in grams		2.3381	1.7209	194.46	261.093	172.154	3,036.13

Table 4 presents a meal containing 0.917 gm. calcium oxide. This meal was ingested by W. D., a normal subject 24 years of age. Chart I is a graph, showing blood-calcium figures before the ingestion of this meal and each hour thereafter for three hours. After studying the graph one may conclude that there is no effect on the blood calcium following the ingestion of food containing 0.917 gm. calcium oxide.

TABLE 9

Case R. L. D. Protocol of blood-calcium percentage before the ingestion of meals (table 8) and during a 24-hour period

HOUR	CALCIUM OF BLOOD
	mgm. per 100 cc.
8:00 A.M. Fasting stomach	10.3
8:30 A.M. Breakfast	
12:00. Noon	11
12:30 P.M. Dinner	
4:00 P.M.	11.3
5:00 P.M. Supper	
8:00 P.M.	10.9
8:00 A.M. Fasting stomach	10.9

TABLE 10

Case A. Z. Protocol of blood-calcium percentage before the ingestion of meals (table 8) and during a 24-hour period

HOUR	CALCIUM OF BLOOD
	mgm. per 100 cc.
8:00 A.M. Fasting stomach	9
8:30 A.M. Breakfast	
12:00. Noon	10
12:30 P.M. Dinner	
4:00 P.M.	9.2
5:00 P.M. Supper	
8:00 P.M.	10.5
8:00 A.M. Fasting stomach	11

Five days later the same subject was given a meal (table 6) containing 1.803 gm. calcium oxide; this was an excessive calcium diet, and its effect on the blood calcium concentration may be noted by referring to chart II and table 7. The peak of the blood-calcium curve was reached about three hours after the meal was ingested, after which it began to recede.

The next experiments were on two normal subjects who were given

CHART I.

(SUBJECT W.D.) CALCIUM OF SERUM BEFORE AND AFTER INGESTION OF MEAL

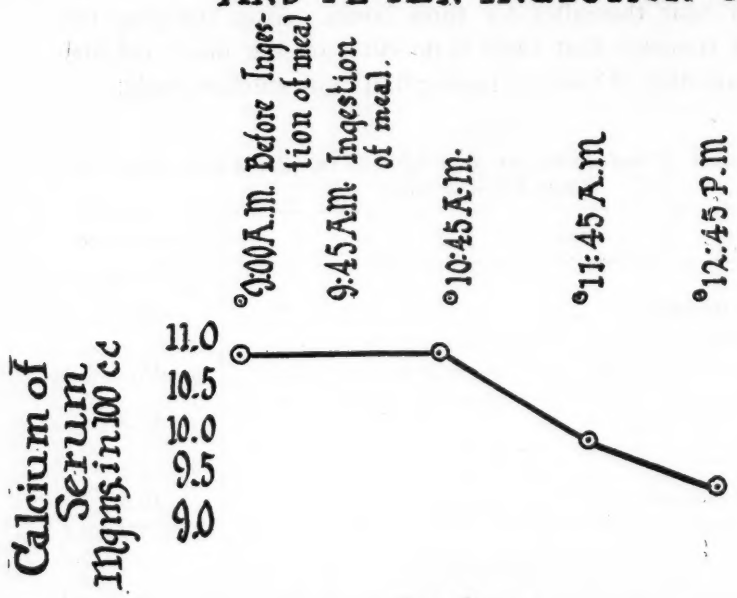


CHART II

(Subject W. D.) Calcium of Serum before and after ingestion of diet with excessive Calcium

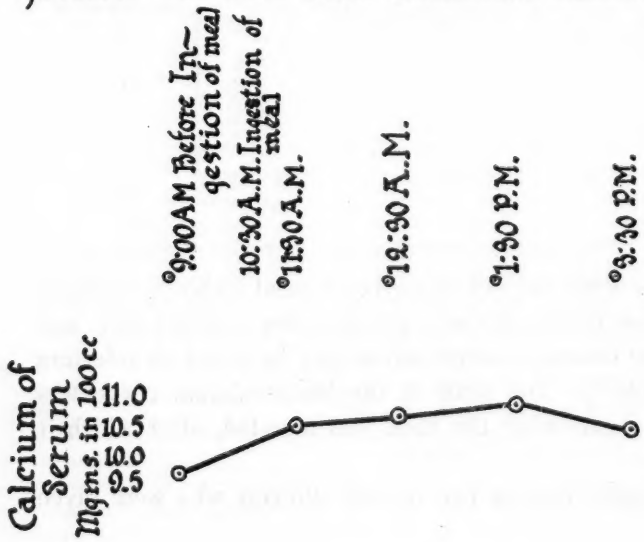


CHART III

Calcium of Serum during a 24 hour period. Meals containing 2.938 grams Calcium Oxide (Table VIII)
(Normal Subject H.L.D.)

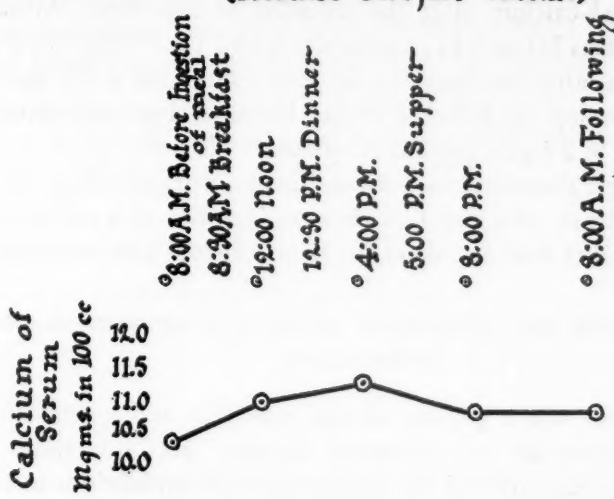
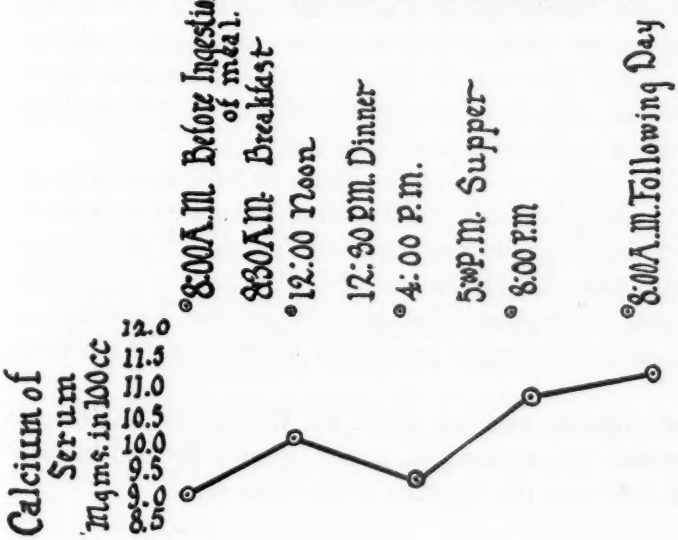


CHART IV

Calcium of Serum during a 24 hour period.—
Meals containing 2.938 grams Calcium Oxide (Table VIII)
NORMAL SUBJECT A.Z.



three meals having a calcium content of 2.338 gm. calcium oxide. Observations were made of the rate of absorption of the calcium of the food, by studying the blood-calcium concentration over a period of 24 hours. The reader will note that cases R. L. D. and A. Z. show an increase of blood calcium after the ingestion of this diet. Attention is invited to charts III and IV, and tables 9 and 10. These show that normal subjects, after the ingestion of food containing 2.338 gm. calcium oxide, develop an increase of the blood-calcium concentration, ranging from 1 to 2 mgm. per 100 cc. serum.

These findings, therefore, do not confirm the work of Clark, or that of Denis and Minot, who maintain that the ingestion of a calcium-poor or calcium-rich diet does not affect the blood-calcium concentration.

4. ABSORPTION AND UTILIZATION OF CALCIUM OF FOOD IN THE TUBERCULOUS

The conditions which govern calcium retention and assimilation in pathological states are not definitely known. McCann states that more calcium is required for the maintenance of equilibrium in tuberculous than in normal subjects. Ott, as well as Mayer, in mineral-metabolism experiments on cases of tuberculosis, showed that there was always a small plus balance of calcium. Croftan, Voorhoeve, Sarvonat and Rebattu maintain that tuberculosis is accompanied by an abnormal loss of calcium.

Having found that normal subjects, after the ingestion of food containing 2.338 gm. calcium oxide, showed an increase of the blood calcium, it was then decided to have several cases of chronic pulmonary tuberculosis placed on the same diet (table 8) in order to see whether there would be a variation in the calcium metabolism.

In the case of W. L. M., one of chronic advanced pulmonary tuberculosis with unfavorable prognosis, there was no absorption of the calcium of the food, and the blood did not show any increase of the calcium content. Chart V and table 11, the case of C. P. O., one of moderately advanced quiescent pulmonary tuberculosis, show that following the ingestion of the same diet there is practically no increase of the blood calcium.

Chart VI and table 12, the case of W. H. W., age 29, one of pulmonary tuberculosis, far advanced-B, active, show a decided increase of blood calcium following the ingestion of the same diet.

Case L. W., age 37, with chronic pulmonary tuberculosis, far advanced-B, active, showed a slight rise in blood calcium following the ingestion of the diet. Case R. H. C., one of chronic pulmonary tuberculosis, far advanced-C, active, showed a rise of blood calcium after the ingestion of the same diet.

May observes that there is no evidence of any serious interference with protein or carbohydrate absorption in tuberculosis, and that the

TABLE 11

Case C. P. O. Protocol of blood-calcium percentage before the ingestion of meals (table 8) and during a 24-hour period

HOUR	CALCIUM OF BLOOD
	mgm. per 100 cc.
8:00 A.M. Fasting stomach	10.5
8:30 A.M. Breakfast	
12:00. Noon	10.5
12:30 P.M. Dinner	
4:00 P.M.	10.2
5:00 P.M. Supper	
8:00 P.M.	10.3
8:00 A.M. Fasting stomach	10.3

TABLE 12

Case W. H. W. Protocol of blood-calcium percentage before the ingestion of diet (table 8) and during a 24-hour period

HOUR	CALCIUM OF BLOOD
	mgm. per 100 cc.
8:00 A.M. Fasting stomach	9.2
8:30 A.M. Breakfast	
12:00. Noon	11.8
12:30 P.M. Dinner	
4:00 P.M.	11.9
5:00 P.M. Supper	
8:00 P.M.	11.2
8:00 A.M. Fasting stomach	11.5

utilization of food is normal. Austin, Ordway and Montagu maintain that when there are no intestinal lesions the capacity of the alimentary tract to handle even excessively large quantities of food seems not to be impaired in pulmonary tuberculosis.

To the above may be added our observations, that in pulmonary tuberculosis the ingestion of food containing 2.338 gm. calcium oxide is

CHART V

Calcium of Serum during a 24 hour period.
Meals containing 2.398 grams Calcium Oxide.
TUBERCULOUS SUBJECT C.P.O.

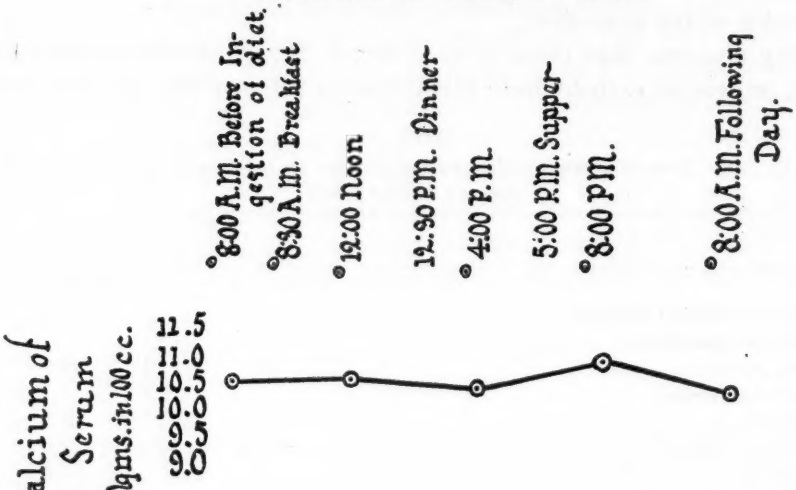
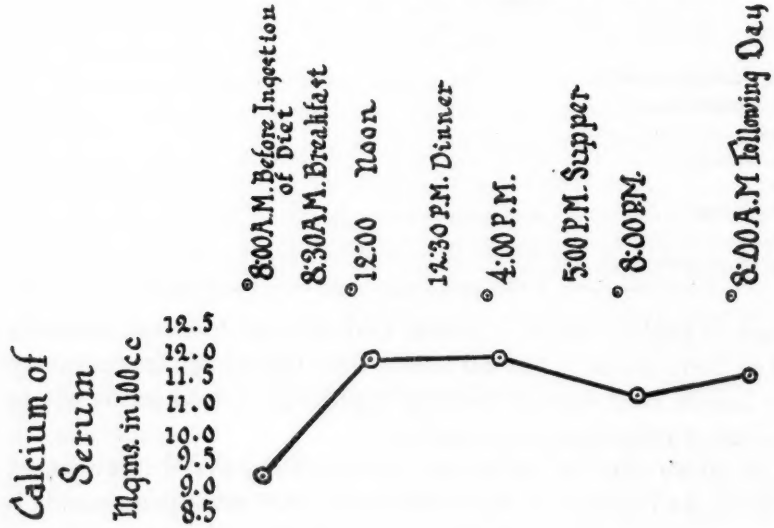


CHART VI

Calcium of Serum during a 24 hour period. Meals containing 2.398 grams Calcium Oxide.
TUBERCULOUS SUBJECT W.H.W.



followed by an absorption of the calcium, and results in an increase of the calcium concentration of the blood. The two cases which did not show an increase of the calcium content of the blood might have had some condition which caused an impaired absorption and utilization of the calcium of the diet.

5. INGESTION AND ABSORPTION OF CALCIUM SALTS AND THEIR EFFECT ON BLOOD-CALCIUM CONCENTRATION

The empirical use of calcium salts in pulmonary tuberculosis is quite common, but based on the claims of observers, who maintain that pulmonary tuberculosis is accompanied by a lowered calcium content of the blood and tissues and that the administration of calcium salts restores to the body the element it so vitally needs.

There is a great deal of controversy regarding the action of the calcium salts and their effect on the body, following oral or intravenous administration. Kost, as the result of feeding soluble inorganic calcium salts to rabbits for a long period, found increased calcium in the bones of the animals as compared with controls. Voorhoeve maintains that calcium administration in man increases the calcium store of the tissues and blood. Heubner and Rona state that intravenous injections of calcium salts in cats will double and triple the calcium content of the blood; this, however, returns to normal within two hours. Wersen administered calcium lactate by mouth to 20 children with tuberculous peribronchial lymph nodes, and studied them by fluoroscopy along with an equal number of untreated controls. He believed that a larger number of the treated cases showed calcification of the nodes, together with a greater improvement in health.

Wells says that it is problematical whether the administration of lime salts in any form or by any route will increase the rate of calcification. The experiments of Tanaka show that injected lime salts may temporarily increase the calcium content of the blood, yet it has not been demonstrated that feeding of the salts will modify the blood calcium in tuberculosis. Denis and Minot did not find any increase of calcium in the blood of normal persons given calcium lactate by mouth, 6 gm. per day, for six to ten days. Muggia was also unable to raise the calcium content of the blood by administering inorganic calcium salts.

It is thus seen that opinions differ with regard to the pharmacological

action of the calcium salts. It was therefore decided to administer calcium salts to normal and tuberculous subjects, and ascertain the effect on blood-calcium concentration.

Following the ingestion of 1.25 gm. calcium lactate by three normal subjects, it was noted that there was very little change in the calcium content of the blood. The ingestion of 2 gm. of calcium lactate by two normal subjects resulted in a slight rise of the blood calcium at the end of an hour, which was followed by a recession to normal within two hours. The ingestion of 1 gm. calcium chloride by three normal subjects showed a gradual increase of the blood calcium, the rise lasting for three hours or more. It was noted that calcium chloride was more readily absorbed, and resulted in a greater blood-calcium concentration than after calcium lactate, and following its ingestion the calcium content of the blood was increased for a longer period than was the case after the ingestion of calcium lactate.

TABLE 13

Case V. J. F. Age 28

DATE	CALCIUM OF BLOOD
	mgm.
3/ 8/24 Before ingestion of calcium lactate	9
3/19/24 After 11 days' calcium lactate therapy (1.3 gm. daily)	11
4/22/24 After 44 days' calcium lactate therapy (1.3 gm. daily)	11.5

The ingestion of calcium lactate by two tuberculous subjects resulted in a decided absorption of the calcium salt, as demonstrated by an increase of the blood-calcium concentration. Chart VII and table 13 show the result on a tuberculous subject of the ingestion of 1.3 gm. calcium lactate daily for 44 days. The rise of the blood calcium was gradual and persistent. These laboratory experiments prove, therefore, that in cases of tuberculosis, the administration of calcium salts is followed by their absorption, as shown in the rise of the calcium-content of the blood.

Healing in tuberculosis is accompanied by the deposition of lime salts in and around the tubercle, this calcium being derived from the blood. If the blood calcium could be kept at all times at a point of saturation by the ingestion of inorganic calcium salts, we would have an ideal condition of the blood for the calcification of the tuberculous lesions. The administration of calcium salts causes the blood calcium to rise to a point of saturation.

It would appear, therefore, that after analyzing the observations herein recorded, there is justification for the use of calcium therapy in pulmonary tuberculosis and that the administration of inorganic calcium salts, more especially calcium chloride, is an ideal therapeutic measure for this condition.

6. THE EFFECT OF THE INGESTION OF CALCIUM SALTS ON THE BLOOD-CALCIUM CONCENTRATION FOLLOWING THE ADMINISTRATION OF CODLIVER OIL

Smith, in the AMERICAN REVIEW OF TUBERCULOSIS, says that the tubercle being normally the seat of calcium deposit, and this calcification being regarded as a means of arresting the disease, the possibility arises that codliver oil, by increasing the calcium metabolism in the tuberculous as it does in the rachitic organism, may cause a deposition of lime salts in the tuberculous foci. However, Smith found that after the intravenous administration of calcium lactate along with the feeding of codliver oil, the life of the tuberculous guinea pig was shortened, and the tuberculous process spread rapidly. His explanation is that the calcium lactate possibly lowers the resistance of the animal and causes a spread of the disease.

Codliver oil, when given in rachitis and allied conditions, so alters the metabolism of calcium as to effect a positive calcium balance. McCollum and his collaborators have found that codliver oil possesses food accessories which have a regulatory influence over the calcium metabolism of the body, having to do especially with calcium deposition.

Hess, in recent studies on rachitis, observes that upon the administration of codliver oil there follows an accelerated rate of recalcification of the bones of the body. The action of codliver oil is due probably to vitamine A or a substance similar to it.

Howland and Park recently have observed the deposition of calcium in bones following the administration of codliver oil in human beings, which is quite perceptible after codliver oil therapy for three weeks. Their explanation is that codliver oil promotes in some way the mobilization of phosphorus in the blood, which in turn stimulates calcium metabolism.

Bethke, Steenbock and Nelson, in experimental work on rats, observed that the animals on a basal diet, containing 105 mgm. of calcium

and 655 mgm. of phosphorus per 100 gm. of ration, showed a marked increase of growth upon the addition of codliver oil to the ration.

Steenbock, Hart, Jones and Black, in experimental work on chickens suffering from rickets, observed that the administration of codliver oil, freed from vitamine A by aeration, caused the calcium of the blood to be restored to normal. These observers maintain that other vitamines, besides fat-soluble A, are responsible for the restoration of normal calcium metabolism.

It is thus seen that the literature is in accord with the view that codliver oil stimulates calcium metabolism, and causes an increased calcium concentration of the blood.

The effect of the ingestion of codliver oil on the absorption of calcium lactate was illustrated in the case of L. T., a normal subject 30 years of age, who was given 1.3 gm. calcium lactate. This resulted in an ap-

TABLE 14

Protocol of calcium of serum before and while ingesting codliver oil

DATE	CALCIUM OF SERUM
	mgm. per 100 cc.
4/ 9/24 Before ingestion of codliver oil	10.6
4/11/24 Before ingestion of codliver oil	10.4
4/14/24 Before ingestion of codliver oil	10.8
4/22/24 While ingesting codliver oil	11.8
5/ 6/24 While ingesting codliver oil	11.7
5/13/24 While ingesting codliver oil	11.5

preciable rise of the blood calcium, the latter going from 10.3 to 11.5 mgm. in two hours. This subject was then placed on codliver oil for one month, at the end of which time he was given 1.3 gm. calcium lactate. This resulted in an increase of the blood calcium from 11.5 to 12.7 mgm. in one hour. Chart VIII and table 14 show that L. T., a normal subject, gives distinct evidence of increased blood-calcium concentration following the administration of codliver oil for about four weeks.

These experiments show that in a normal subject the blood calcium is increased after the ingestion of codliver oil. Furthermore, the administration of an inorganic calcium salt, such as calcium lactate, together with the ingestion of codliver oil, results in a much higher blood-calcium concentration than after the ingestion of the calcium salt alone.

CHART VII (CASE V.J.F. AGE 28)

Diagnosis-Tuberculosis, Pulmonary, Chronic, Moderately Advanced-B, Active

Calcium of Serum Before and while ingesting 1.3 Grams Calcium Lactate daily over a period of 44 days

°Before Ingestion of Calcium Lactate 3/8/24	°After 11 Days Calc. Lactate Therapy 3/19/24	°After 44 Days Calcium Lactate Therapy 4/22/24

CHART VIII

(CASE L.T. NORMAL SUBJECT, AGE 30)

Calcium of Serum before, and while ingesting Cod Liver Oil.

7. RELATIONSHIP OF COAGULATION TIME TO CALCIUM CONTENT OF BLOOD

The question of coagulation time in pulmonary tuberculosis is of vast importance, owing to the fact that in a great many cases of persistent hemorrhage the cause may be an increased coagulation time of the blood.

TABLE 15

Relationship of coagulation time of blood to calcium of serum in normal subjects

NUMBER	SUBJECT	CALCIUM OF SERUM	COAGULATION TIME
		mgm.	*minutes*
1	L. T.	11.5	3
2	W. D.	10.9	3
3	B. A. S.	10.6	3
4	F. B.	10.5	3.5
5	R. L. D.	10.3	3
6	C. J. S.	10	4.5
7	W. P.	9.4	4.5
8	W. H. P.	9.1	4.5
9	A. L.	9	3

TABLE 16

Figures of average calcium content and coagulation time of patients in different stages of pulmonary tuberculosis

	CALCIUM OF SERUM	COAGULATION TIME
	mgm.	*minutes*
Tuberculosis, chronic, pulmonary, apparently arrested (6 cases)	10.78	3.3
Chronic pulmonary tuberculosis with moderate amount of lung involvement, clinical activity not pronounced (20 cases).....	10	4
Chronic pulmonary tuberculosis, advanced, with large amount of lung involvement and with history of hemorrhages (9 cases).....	9.25	4.5
Chronic pulmonary tuberculosis, advanced, with large amount of lung involvement and with no history of hemorrhages (20 cases).....	9.25	5.4
Chronic pulmonary tuberculosis, with chronic parenchymatous nephritis (4 cases).....	9.22	4.1

The use of calcium salts in cases of pulmonary hemorrhage has been quite extensive, because it was thought that many of these cases were the result of a decrease of the calcium content of the blood, and the administration of calcium would benefit the condition. Many observers maintain that there is no relationship between the coagulation time and the calcium content of the serum, and that furthermore the administration of calcium salts does not decrease the coagulation time.

Maver and Wells maintain that the coagulation time does not seem to be altered in tuberculosis, except when shortened after large hemorrhages. Solis-Cohen found that in human tuberculosis the coagulation time has generally been somewhat more rapid than normal. Sweany, Weathers and McCluskey found that the coagulation time is slightly increased in pulmonary tuberculosis.

It was, therefore, decided to make a number of observations on both normal and tuberculous subjects, studying the coagulation time and the calcium content (tables 15 and 16). A number of observations were also made in normal and tuberculous subjects on the calcium content of the serum and coagulation time, before and after the ingestion of calcium salts (tables 17 and 18).

The method of estimating the coagulation time of blood used at this hospital is that of McGowan. Glass capillary tubes, 1 mm. in diameter and 150 mm. long, are filled with blood, and small sections are broken off at intervals of 30 seconds until a fine filament of fibrin is observed between the carefully separated ends of the tube and fragment. In normal subjects the coagulation time varies from 1 to 5 minutes.

In studying tables 15 and 16 it is found that the coagulation time in normal as well as in tuberculous subjects is within normal range. These tables also show that, as a general rule, the higher the blood-calcium concentration, the shorter the coagulation time. This tendency is also noted after the administration of calcium salts.

8. THE EFFECT OF THE INGESTION OF CALCIUM SALTS ON THE COAGULATION TIME IN NORMAL AND TUBERCULOUS SUBJECTS

Maver and Wells found in their work on guinea pigs that animals fed calcium showed a longer coagulation time than those not so fed. The tuberculous animals that were not fed calcium showed a much longer coagulation time than did the normal animals. The calcium-fed guinea pigs with tuberculosis had a more rapid coagulation time than the tuberculous ones not fed calcium.

Charts IX and X and tables 17 and 18 demonstrate the following:

1. The oral administration of calcium salts is accompanied by an increase of the blood calcium.

2. With the increase of blood calcium there is an accompanying decrease of the coagulation time.

Table 19 and chart XI show that the oral administration of 1.3 gm. calcium lactate daily for 11 days resulted in a gradual decrease of the coagulation time of a tuberculous subject.

DISCUSSION

Observations on the blood of both normal and tuberculous subjects show that there is very little variation in the calcium content of the

TABLE 17

Protocol of blood-calcium percentage and coagulation time before and after the ingestion of 1 gram calcium chloride per mouth

	CALCIUM OF BLOOD	COAGULATION TIME
	mgm.	*minutes*
Fasting stomach	9.7	3.3
1 gm. calcium chloride		
1 hour	10.8	2.8
2 hours	10.9	2.8
3 hours	11	2.8

TABLE 18

Protocol of blood-calcium percentage and coagulation time before and after the ingestion of 1.3 grams calcium lactate per mouth

	CALCIUM OF BLOOD	COAGULATION TIME
	mgm.	*minutes*
Fasting stomach	9	3.5
1.3 gm. calcium lactate		
1 hour	12.3	2
2 hours	8.7	1
3 hours	11.0	0.75

TABLE 19

Protocol of coagulation time in minutes before and during the ingestion of 1.3 grams calcium lactate daily over a period of 11 days (Case V. J. F. Age 28)

DATE	COAGULATION TIME
	minutes
March 8/24	3.5
March 9/24	3
March 10/24	2
March 11/24	2
March 12/24	2
March 13/24	2.5
March 19/24	3

serum. The contention of various observers, that tuberculosis is accompanied by a diminution of the calcium of the blood, cannot be confirmed.

CHART IX

Average blood Calcium concentration and coagulation time before and after the ingestion of 1 gram Calcium Chloride (Average Figures Obtained in three Normal Subjects)

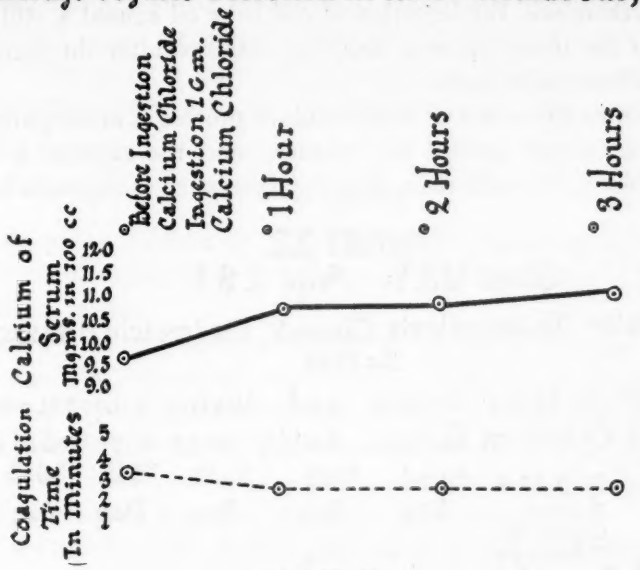
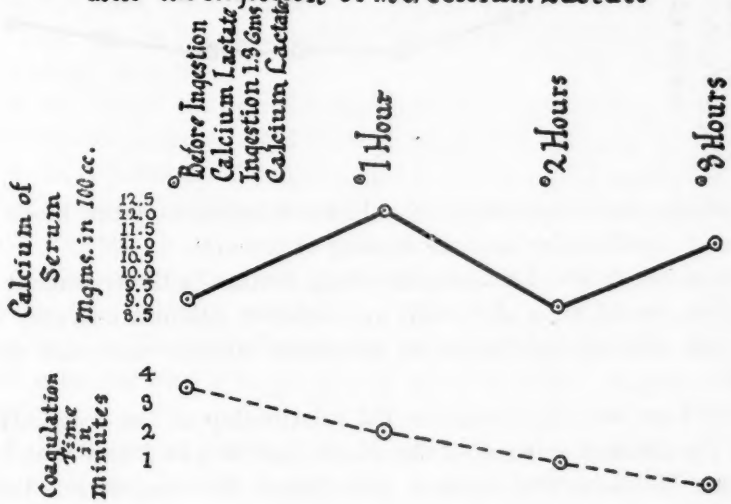


CHART X

(Case V.J.F. Age 28)

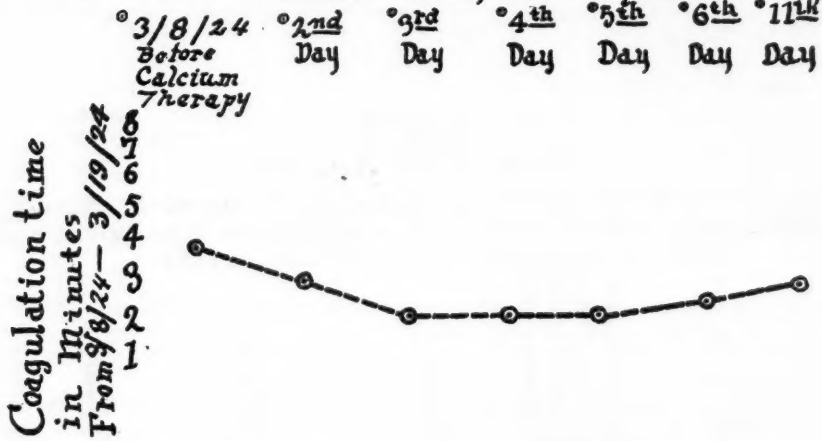
Diagnosis-Tuberculosis, Chronic, Moderately Advanced-B, Active. Blood Calcium concentration and coagulation time before and after the ingestion of 1.3G. Calcium Lactate



Ingestion of a number of diets with a varied calcium content, as well as the ingestion of inorganic calcium salts in both normal and tuberculous subjects, resulted in an increase of the blood-calcium concentration. Furthermore, the ingestion of cod liver oil caused a still greater increase of the blood calcium than was obtained after the ingestion of food or calcium salts alone.

Inasmuch as the arrest of a tuberculous process is accompanied by a calcification in and around the tubercle, and the calcium is derived from the blood, it would seem that any system of therapeusis in tuber-

CHART XI
(Case V.J.F. Age 28)
Diagnosis- Tuberculosis, Chronic, Moderately Advanced-B, Active
Coagulation time before and during ingestion of 1.9 Grams Calcium Lactate daily over a period of 11 days.



culosis which results in a state of calcium saturation of the blood is conducive to calcification and the healing of tubercle.

It is therefore believed that an important feature in the treatment of tuberculosis would be a diet with an excessive calcium content, together with the administration of inorganic calcium salts and cod-liver oil.

Observations were also made on the relationship of the coagulation time to the calcium content of the blood, and it was found that the higher the blood-calcium content, the shorter the coagulation time.

Furthermore, it was noted that the ingestion of inorganic calcium salts resulted in a decrease of the coagulation time. It therefore follows that cases of pulmonary hemorrhage, in which there is an increase of the coagulation time, would be benefited materially by such therapy.

Inasmuch as our studies show that the oral administration of calcium salts is followed by a rapid rise of the blood calcium, it would appear that indiscriminate intravenous injections of these salts are unnecessary.

SUMMARY

1. The serum calcium of normal subjects, whose ages ranged from 16 to 43 years, varied from 9 to 12 mgm., with an average of 10.28 mgm. per 100 cc. serum.

2. There was very little variation of the blood calcium in the different stages of pulmonary tuberculosis. The lowest average figure, that of 9.22 mgm., was noted in cases of chronic pulmonary tuberculosis complicated by chronic parenchymatous nephritis. The highest average blood-calcium concentration, that of 10.78 mgm., was obtained in cases of apparently arrested pulmonary tuberculosis.

3. Cases of advanced chronic pulmonary tuberculosis with history of hemorrhages, as well as those without hemorrhages, had identically the same blood-calcium concentration, that of 9.25 mgm.

4. In a normal subject the ingestion of a diet with a calcium-oxide content of 0.917 gm. did not result in an increase of the blood-calcium concentration. The ingestion of a diet with a calcium-oxide content of 1.803 gm. in the same subject resulted in an appreciable increase of the blood calcium.

5. In normal subjects the ingestion of a day's diet containing 2.338 gm. calcium oxide resulted in an increase of the calcium of the blood.

6. In 5 tuberculous subjects the ingestion of the same diet resulted in a blood-calcium increase in 3, while no apparent change was noted in 2 subjects.

7. The ingestion of inorganic calcium salts, both in normal and tuberculous subjects, resulted in a rise of the calcium concentration of the blood. The rise following the use of calcium chloride was greater, and extended over a longer period than after the ingestion of calcium lactate.

8. In a normal person on a regular diet the ingestion of codliver oil stimulated calcium metabolism, and resulted in an increase of the blood-calcium concentration.

9. The ingestion of both an inorganic calcium salt and codliver oil was followed by a much higher blood-calcium concentration than the ingestion of the calcium salt alone.

10. A study of the coagulation time in normal and tuberculous subjects revealed the fact that there was practically no variation. As a general rule, it was found that the greater the blood-calcium concentration, the shorter the coagulation time.

11. The administration of calcium salts resulted in a decrease of the coagulation time, together with an increase of the calcium content of the blood.

12. In a tuberculous subject, the administration of 1.3 gm. calcium lactate daily, over a period of eleven days, resulted in a decrease of the coagulation time of the blood.

Acknowledgment is here made of the hearty coöperation of Dr. R. L. Cook, Medical Officer in Charge, as well as of his encouragement of these investigations. I am indebted to Dr. A. G. Walker, Clinical Director, for many helpful suggestions and to the other medical officers for their coöperation. Acknowledgment is also made of the assistance of Miss Lula Stork, Assistant Laboratorian in Bacteriology, as well as of Miss C. R. Clancy, Chief Dietitian of the Hospital. Dr. R. L. Thompson, of the Thompson Sanatorium, Kerrville, Texas, was kind enough to allow the use of some of the clinical material at his institution.

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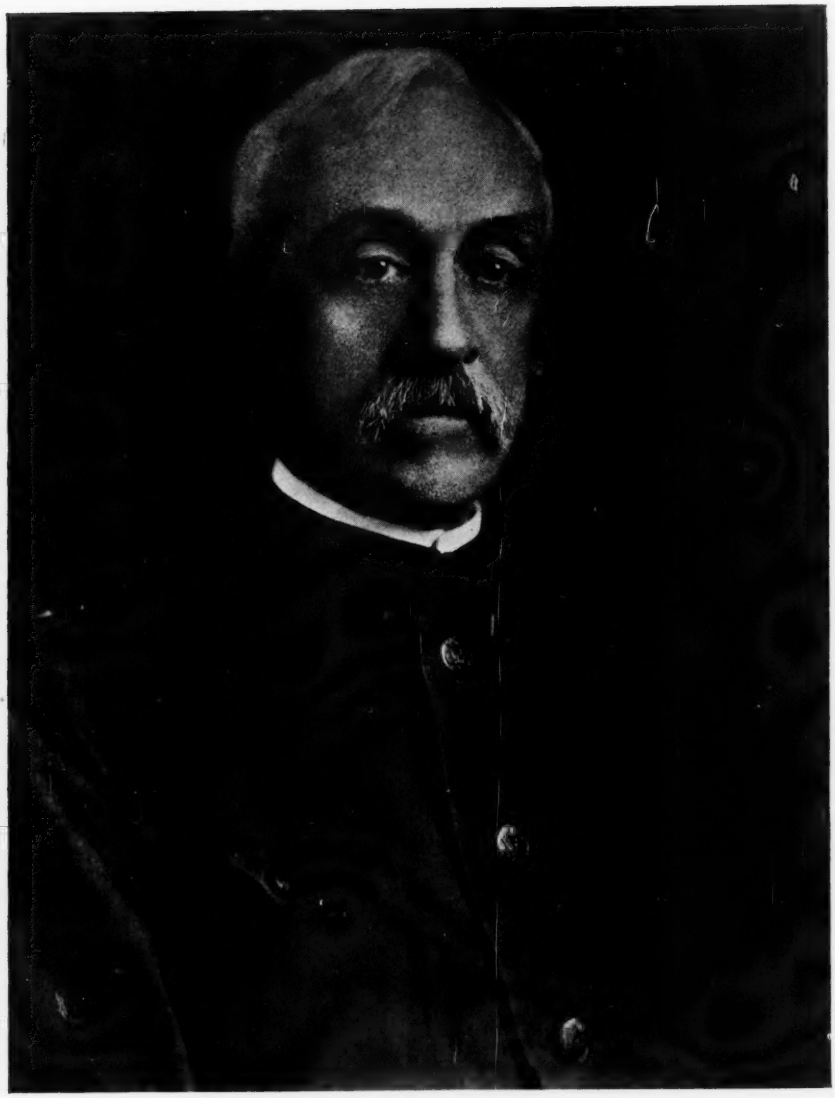

George E. Bushnell
1853-1924

Colonel Bushnell

An estimate of his character and work[1]

In 1908, I was assigned to the Army Tuberculosis Hospital at Fort Bayard for duty. I was sent there primarily to recover from tuberculosis, and as I traveled westward from Washington I was hopeful, and looked forward with pleasant anticipation to an active out-of-door life on the western plains, hunting, horseback riding and roughing it. This way of curing tuberculosis appealed to me. I arrived at my new post and was met at the station by a young medical officer, from whom, as we drove in an army buckboard to the hospital, I learned for the first time of Colonel Bushnell's methods of treating tuberculosis. To me the news of the treatment came as a greater shock than had my tuberculosis diagnosis. I was put to bed, Colonel Bushnell my doctor. From then I was to learn a great deal concerning him. It was a hard struggle to relinquish my ideas of the cure of tuberculosis and yield to the monotonous, hibernating methods of my doctor. I had not learned as yet the truth of Trudeau's saying, "Conquer fate by acquiescence." My obstinacy was met with patient reasoning and convincing talks until I was finally converted to the rest cure. I recovered, but without the wonderful personality and guidance of Colonel Bushnell it might have been otherwise. After recovery it was my good fortune to serve under him for over ten years. Over eight years of this period was spent at Fort Bayard and the remainder at Washington in the Surgeon-General's Office during the War.

I shall treat very briefly Colonel Bushnell's previous career, of which I can speak only by hearsay and from official records of the War Department. George Ensign Bushnell was born in Worcester, Massachusetts, September 10, 1853. He was graduated with the degree of A.B. from Yale in 1876, and then attended the Yale Medical School and was graduated in 1880. While serving as interne in a New York hospital he developed the first manifestations of pulmonary tuberculosis, a disease which played such an important part in his future life. The first symp-

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toms were slight, soon disappeared, and were not taken seriously. In February, 1881, he was commissioned a First Lieutenant and Assistant Surgeon in the United States Army, and was first stationed at Fort Yates, Dakota. After this he served at Fort Ellis, Montana, and Fort Snelling, Minnesota. No doubt his frontier service built up his resistance and kept his tuberculosis latent. It was a life full of adventure, and one over which he loved to reminisce in his later days. I remember his telling of being surgeon in charge of 3,000 Sioux Indians, prisoners of war. Before leaving he was asked to go out and meet them all, and in the centre of this circle of 3,000 Indians he was presented with a buffalo rug in appreciation of his care of them. He was then stationed at Fort Preble, Maine, Camp Pilot, Butte, Montana, Fort McKinney, Wyoming, Fort Hamilton, New York, Fort Assinniboine, Montana, and was on duty at Boston, Massachusetts, and at the Surgeon-General's Office during the Spanish-American War. Under the strain of wartime work his health failed, and pulmonary tuberculosis was definitely diagnosed. He obtained six months' sick leave and went to Asheville, North Carolina, where he came under the care of Dr. Charles L. Minor and learned from this noted specialist the treatment of tuberculosis. He improved sufficiently to return to duty at the end of his sick leave and was then stationed at Fort Logan, Colorado, for two years. During this time he came under the care of one other prominent internist and tuberculosis specialist, Doctor Carroll E. Edson, of Denver. I have heard Colonel Bushnell speak many times of his gratitude to his physicians for their advice and views regarding that form of the treatment of tuberculosis which he was later to introduce and carry out so effectively at Fort Bayard.

In August, 1903, Colonel Bushnell was ordered to Fort Bayard, and in May, 1904, became Commanding Officer of that hospital. At that time the present day treatment of tuberculosis—of which Trudeau was the pioneer in this country, and which Minor was employing at Asheville and Edson at Denver, at the beginning of Colonel Bushnell's illness—had not been perfected at Fort Bayard. Patients were not resting enough or living out-of-doors as much as they should. Many were laboring under the delusion that the rarefied atmosphere of high altitudes, the dryness of the air, and the abundance of sunshine were the principal part of the cure, that breathing exercises were indicated, or that roughing it on a ranch was the proper plan. Overeating, drinking large quantities of milk, and swallowing raw eggs was another fallacy

that prevailed at that time; likewise, the use of alcoholic beverages. I am told that under one Commanding Officer, alcoholic drinks of all kinds were freely prescribed for the patients at Fort Bayard. They evidently had false ideas about their treatment; they were prejudiced. Tuberculosis is a disease that often heals in spite of any treatment. Cases already fibrous, or cases wrongly diagnosed are ever present in proof and defense of any method of treatment. Perhaps the Army Surgeons before Colonel Bushnell's time knew the sound principles of tuberculosis therapy, but had been unable to convince and influence their patients. It required the personality, the ingenuity and perseverance of Colonel Bushnell to do this. He had recovered from the disease himself, and was a living example of a cure due to rational treatment. He went among the patients and talked to them individually. The treatment was so different from what they wanted to do, it required such determination and will power on their part to carry it out, that they were skeptical. Finally, volunteers were obtained from some of the more coöperative and intelligent patients. Hospital tents were erected, and these patients began the open-air, rest cures under the direct supervision of Colonel Bushnell. The results were so striking that all the other patients learned about it. More volunteered, open-air porches were added to the buildings, new open-air wards were gradually constructed, and finally the out-of-doors, rest treatment became a tradition of Fort Bayard, which, thereafter, was always carried out with remarkable faith and enthusiasm.

When I arrived at Fort Bayard in 1908 Colonel Bushnell had been Commanding Officer for four years. My journey for several days through a desert waste, and my drive of three miles from the station over dry, desolate foothills, had certainly not prepared me for the sight of the hospital, situated as it was in a veritable oasis in the desert, studded with shade trees, green lawns, shrubbery, and flowers. How refreshing and pleasing was such a scene, and what a credit to its maker! In this one spot one man had made the desert bloom like a rose. Colonel Bushnell commanded Fort Bayard for thirteen years, and during that time he accomplished much which speaks for his remarkable knowledge of many things. The reservation was enlarged to twenty square miles, to include valuable springs, and to assure ample water supply for beautifying the hospital grounds. Being a great lover of nature, and having a good knowledge of botany, Colonel Bushnell spent much of his time, when not attending the sick, riding over the reservation. He had an

excellent understanding of forestry and agriculture, especially horticulture. Trees and shrubbery were raised from seed, and the landscape gardening was all done under his supervision. Vegetable gardens, a chicken ranch, fruit farms, a piggery, a dairy, cattle raising were among his activities, and he took a keen interest in every detail of this work. The beginning of the day found him up early, inspecting work being done about the hospital grounds. From eight to eleven he was usually to be found at his office, where he attended to the administrative work of the hospital, and then followed several hours which he devoted to his patients. In the afternoon be busied himself in his office, about the hospital, or more frequently out-of-doors, riding over the reservation, working among his flowers, or supervising the planting of trees and shrubbery, or perhaps taking long walks, from which he seemed to derive much pleasure.

He turned with ease from one thing to another. All spare moments were spent in improving his mind. His evenings were devoted to study, for he was a great student and reader. His exceptional memory enabled him to retain for ready use a wealth of learning on many subjects. He was probably one of the greatest scholars in tuberculosis of his time. He spoke French, German and Spanish, translated German, French, Italian, Spanish, Latin, Greek and Sanskrit, and read French, German, Italian and Spanish readily. While at Yale, he and President Hadley (his classmate) were the only two in the class who studied Sanskrit. With this knowledge of languages he was able to keep in touch with the tuberculosis work in foreign countries and in this way gained considerable information from foreign literature, especially German. His devoted wife, being likewise highly cultured, was a deeply interested companion in his study and reading. He usually conducted classes in medical German for any of his officers who cared to join, and if any of us became interested in any special subject he was always generous with his assistance, translating and abstracting long articles. We often wondered how he found time for so much work. Each year he delivered a course of lectures on tuberculosis to his officers, and these lectures were carefully prepared and were kept up to date by a thorough survey of medical literature. They were first held in the early afternoons, but later, when he saw that some were inclined to be a bit sleepy at that hour, he changed them to the evening and quizzed us over the previous lecture. Needless to say, we had to remain wide-awake, but to those of us who were interested in the specialty of tuberculosis, and were only

too eager to absorb all the information we could, this required no effort. All medical officers, however, were not concerned with this branch of medicine, especially the phthisiophobiacs, who did not wish to come in contact with consumptive patients, and sought administrative duties for this reason.

Colonel Bushnell's views on the subject of tuberculous infection were very decided. As early as 1908, when the dangers of infection and the necessity of preventing infection in tuberculosis were being stressed, he took the stand in his writings and lectures that tuberculosis of the civilized adult was due to reinfection from within, and not exogenous; that the danger from repeated small or massive infections from without existed only in infancy and childhood; and that our campaign against tuberculosis must be aimed more at the maintenance or increasing of the body resistance. He was an early and consistent advocate of this view, and always defended it in a convincing manner. Early in his career as a tuberculosis specialist, he was very much opposed to the diagnostic use of tuberculin, and, in a letter to the Surgeon-General, called attention to the dangers and errors caused by the employment of tuberculin as a diagnostic measure. He recommended its disuse in the Army, and when his letter was referred for remarks to the Commanding Officer of the hospital where tuberculin tests were being used rather frequently, many typewritten pages were submitted in defense of this policy, and numerous quotations from medical books and the writings of eminent internists were cited to prove the diagnostic value of tuberculin. I only mention this to illustrate how quick he was to sense the new developments in his specialty, and yet how sound were his viewpoints, as proved by later developments. Constant study and thought were the factors which made such creative achievements possible, for, although he did very little experimental work himself, he showed remarkable ability and intuition in interpreting the experiments of others. His efforts to have research work carried out along lines which interested him were of little avail under the army system. Frequent change of station of officers on account of foreign service, duty with troops, etc., permitted very little continuity of work. A laboratory officer on duty at Fort Bayard no sooner became familiar and interested in tuberculosis research problems than he was ordered away on foreign or field service. While Colonel Bushnell was a good pathologist and knew laboratory technique, he was Commanding Officer, and his time was necessarily largely occupied by administrative duties. His recommendations regarding tuberculin were supported by the Surgeon-General.

In November, 1909, Colonel Bushnell was granted six months' sick leave, which he spent quietly at Sierre Madre, California. He had not been well, and upon physical examination was told he had some activity at the base of his right lung. While on leave he discovered that the sounds interpreted as pathognomonic of activity were marginal râles, and when he returned to Fort Bayard from leave he made a careful study of these râles, and finally completed a paper on the results of his investigations, entitled, *Marginal Sounds in the Diagnosis of Pulmonary Tuberculosis*. This paper was read before the International Congress of Tuberculosis at Rome, in 1911, where Colonel Bushnell was sent as a representative of the U. S. Army. At this time he spent several months traveling abroad. His work on marginal sounds was only one of many investigations which he made with reference to physical signs in pulmonary tuberculosis. Soon after his return from Europe he investigated, and wrote a paper on extrapulmonary sounds. He was continually studying the acoustics of percussion, the production of various kinds of extrapulmonary sounds, and the origin of vesicular breathing.

During the winter of 1916 and 1917, respiratory infections began to become more frequent in the army, and an unusual type of bronchopneumonia, associated with haemoptysis and persistent râles at the bases, became rather common. Such cases began to arrive at Fort Bayard, diagnosed as tuberculosis. At one Army post it was thought that tuberculosis was occurring in epidemic proportions. One Army surgeon sent to investigate this epidemic, taking for granted that the cases were tuberculous, went so far as to trace its origin to typhoid prophylaxis. Many complications arose, and Colonel Bushnell was sent by the Surgeon-General to investigate the trouble. He arrived, examined the worst cases, and soon demonstrated that they were not tuberculous. The tuberculosis epidemic was a mistake, and everyone heaved a sigh of relief. The personnel at the post was thankful because they all thought they were about to become victims of the "great white plague," and the Surgeon-General's office breathed easy once more because the success of typhoid prophylaxis had received no set back. Respiratory infections with basal râles, which persisted for weeks and months, and were often confused with pulmonary tuberculosis on account of the blood-spitting and chronicity, now began to appear along the Mexican Border, where many of our troops were concentrated. These infections continued up to and throughout the World War, led to many errors in diagnosis, and gave much concern to the medical officers of all armies.

Colonel Bushnell knew all about them. They had been studied clinically and bacteriologically at Fort Bayard, and he was in a position to appreciate the difficulties of army tuberculosis boards in having to quickly differentiate these chest conditions from tuberculosis. He took steps early to prevent errors in diagnosis and not duplicate the experience of the French, which will be discussed later.

Colonel Bushnell once remarked that he believed his greatest usefulness in tuberculosis work had been in being able to tell patients who consulted him that they did not have consumption. He was decidedly a keen diagnostician, particularly in his specialty, and often made a prognosis which differed widely from that made by another, but which frequently proved correct. I learned from experience to respect his views, because he had an uncanny way of usually being right. When officers were ordered to Fort Bayard for duty, they generally went there with a heavy heart. Since it was a tuberculosis hospital, they imagined it would be depressing. It was very much isolated, and the Commanding Officer had the reputation of being exceedingly strict and cranky, neither of which was true. It was not a depressing place, a spirit of optimism prevailed among the patients, and they were for the most part contented and very faithful in carrying out their treatment. Many recovered their health, which made all hopeful. Colonel Bushnell was always optimistic about the disease he treated, and he was strict with the patients, but they all realized it was for their own good and respected his policies. He spared no pains in teaching his patients the treatment of their disease. He made a great point of individualization in treatment: "Our object in treatment is to help the patient cure himself. We are helping the patient, not attacking directly the tubercle bacillus, and, therefore, we must individualize in our treatment," is the way he expressed this idea. In a paper on *The General Management of Tuberculosis* he states, "Docility—willingness to be taught—is one of the important factors in prognosis," and in the same paper he gives his stand on exactness of treatment thus, "Patients should be treated like men and women, not like children, and the responsibility for the proper conduct of their cases should be placed squarely upon their shoulders. The physician is not to be excused who permits harmful exercise or harmful amusements and occupations of any kind, on the plea that otherwise the patient will become homesick and discontented." Nervous patients are always a problem in every sanatorium, and it taxes the resourcefulness and psychological ability of the doctor to keep them calm and

satisfied. To the worrying kind, when everything else failed, he used to make this concession, "Since you say that you cannot help worrying, if you will promise not to worry at other times, I will allow you a 'worrying hour,' say between five and six P.M. In that hour you can set at work to worry just as hard as you like."

The isolation of the hospital brought everyone closer together. It was like a large family, everyone interested in everyone else, and each eager to help the other. While the life there was a simple one, it was far from being dull, and every officer regretted to leave and wished himself back. The Colonel was very exacting and had his irritable moments. If ever an unkind word escaped his lips he regretted it later and always said so. I knew him intimately for more than ten years; many a long walk have we taken together, and many a pleasant evening have I spent by his side. I have seen him angry in his office over official matters, but never at any other time. His real character was not bitter and fault-finding; it was modest and sweet. His wonderful mind bubbled over with good thoughts, and he had a ready wit and a keen sense of humor. In his home he was a most delightful host, and had much to talk about, and an inexhaustible supply of stories. He loved his friends, and, no matter how occupied with important matters or how crowded his days, it was his joy and pleasure to have them in his home. He was never a well man, and struggled with sickness all his later years. In spite of this handicap he accomplished much, and clung to life with grim determination, working diligently and courageously, and never deteriorating mentally. His world was broadened through eyes which reflected a highly developed and cultured brain. During his walks he showed his great love for nature, and had much to say about the flowers, shrubs and trees, or the animal and bird life which he saw.

Returning again to his medical work, my description would not be complete without saying a few words about Colonel Bushnell's interest in body metabolism and his dietetic treatment of certain types of pulmonary tuberculosis. Father Moran, a French priest, who visited Fort Bayard regularly to administer to the sick of his church, and who usually was Colonel Bushnell's guest, during his visits presented the Colonel with a French book on dietetics, by Carton. It was from this book that the idea was obtained that old, fibrous, sluggish and congested tuberculous lesions could be benefited by placing them on a low caloric diet containing very little concentrated food, such as meats, fats, and sugars, and consisting largely of carbohydrates, fresh vegetables, and fruit.

From the very beginning of his tuberculosis work, Colonel Bushnell's views had been along the lines of moderation in eating. To quote from one of his papers:

> As for food, stuffing as a routine practice has been given up by the physician, but not as yet by the patient. One must know when to stuff, when to stop stuffing, when not to countenance it at all. The proletariat of large cities, men who have kept at work too long, mothers who are "too tired to eat," will be benefited for a time by an abundance of plain food. When they are "filled up," as we say in the army, that is, when the dietetic deficiencies are made up, the daily ration should be reduced. The great majority of patients have no dietetic deficiencies to make up, and from the first should be put upon relatively restricted diet, which alone agrees with the resting individual over long periods of time. Most of the miseries of the tuberculous patient are due to overeating, or to an improperly selected diet. He cannot divorce himself from the idea that stuffing is his only salvation. Nothing that is bad for the health is good for tuberculosis in the long run, and this applies to food as a fundamental and universally applicable proposition.

The Carton System not only meant moderation in eating, but it also meant a decided restriction of certain weight-producing foods, a new departure in treatment, and one which the patients did not take to readily. They believed they must eat many calories and keep fat. A loss of a few precious pounds startled them, even though they felt better in so doing. It required considerable courage to introduce a restricted diet among tuberculosis patients, but Colonel Bushnell was able to put it over and obtained some very good results. His enthusiasm probably prejudiced him, for at times his patients caused him to be misled in respect to the benefits of his theories as to diet. In endeavoring to please him, they professed faith in the diet, extolling the wonderful benefits obtained therefrom, when, in fact, they were eating as indiscreetly as ever. The diet became the Colonel's hobby, and, while it failed as a routine procedure, it did counteract to some extent the practice of overeating, and in isolated cases of long-standing fibrous tuberculosis associated with damaged viscera it did bring about improvement in certain symptoms. For a number of years Colonel Bushnell was profoundly interested in the study of body metabolism, and although he never wrote on the subject he was thoroughly versed in this phase of medicine, and never ceased to theorize and ponder over it.

During the early part of 1917, as the war clouds began to gather, Colonel Bushnell saw the probable necessity of examining large bodies

of men as quickly and accurately as possible, and began to plan a standard method of examining the lungs, practical for military requirements and conditions. A simple plan was finally devised. Then ambulatory patients unknown to him were selected and examined according to this plan. Each examination was timed and the accuracy of diagnoses checked. Devoting from one and one-half to three minutes to each chest, lesions could be detected and usually correctly diagnosed. *S.G.O. Circular No. 20*, June 13, 1917, establishing a standard method of examining the lungs for tuberculosis, was based on this work. We entered the World War on April 6, 1917, and two months later, June 2, 1917, Colonel Bushnell was ordered to Washington and placed in charge of all the tuberculosis work of the Army. Just previous to this, the sensational report had reached this country that 86,000 French soldiers had been invalided on account of tuberculosis in the first year of the war. This report had received wide publicity, both in the lay and medical press. This announcement was received with consternation, as we were mobilizing for war and the relatives of our soldiers became much concerned about tuberculosis in the Army, the dangers of tuberculous contagion, and the perils to health of Army service. Numerous letters were received by the Surgeon-General's Office, both from individuals and various tuberculosis organizations, regarding the tuberculosis question. A committee from the National Association for the Study and Prevention of Tuberculosis conferred with the Surgeon-General, and it was decided to reëxamine for tuberculosis troops already mustered into the service. This report was later corrected by the French minister of War, who stated that considerably less then one-half had been found upon reëxamination to have tuberculosis, and Rist reported that even less than 20 per cent really had the disease. However, an exaggerated conception of the prevalence of tuberculosis in the French army had been established, and the impression was difficult to counteract. The Surgeon-General saw that tuberculosis portended to play an important part in the medical problems of the war, and called to his assistance Colonel Bushnell, who, he knew, was well qualified to handle the situation, and at the same time had the confidence of the medical profession and especially the National Tuberculosis Association. Colonel Bushnell hurried to Washington, and was placed in charge of the Division of Internal Medicine. There being prominent internists to take care of the other branches of internal medicine, he devoted all his time to tuberculosis, and General Gorgas gave him a free rein.

Thus began a period of his life which merits a little more detail in my account, for it was during this time that he rose to the greatest heights of his career and came into the most prominence. It was, no doubt, a most busy period. On September 10, 1917, he reached the age of 64, and was retired. On the afternoon of that day, he and Mrs. Bushnell celebrated the event and took a long walk through Rock Creek Park. The next morning he was back on active duty again. There was much to be done. The Army must be rid of cases of active tuberculosis, cases of tuberculosis must be excluded, and suitable hospitalization must be provided for cases developing in the service. *Circular No. 20* was written and published, to standardize the examinations for tuberculosis. Colonel Bushnell appreciated the difficulties and disadvantages of any standard, but he said, "Though imperfect, a standard is better than no standard under the conditions of this examination." *Circular No. 20* became a classic in the diagnosis of tuberculosis in the Army, and has stood well the test of time. In this circular, Colonel Bushnell explained the purpose of the examination, and mentioned how examination for tuberculosis in the military service differed from that of civil practice. Tuberculosis examining boards were quickly organized, made up mostly of internists and tuberculosis specialists. The civilian training camps were examined first, then the large camps of the regular army, and when I reported to the Surgeon-General, as Colonel Bushnell's assistant, in the early part of August, steps were well under way to examine also the National Guard, which had been ordered into the Federal Service. It was planned to examine the latter in their armories and use boards made up from the large number of skilled internists, who were anxious to do something, yet, on account of their health, age, teaching engagements, etc., were unable to leave their homes. This was only partially successful, for before many could be examined the National Guard was ordered into the Southern camps, and it became necessary to form boards in these places. By this time the examination work had progressed far enough to determine some of the difficulties. The examiners were not all equally skilled; some very successful and prominent tuberculosisspecialists were found to be poor diagnosticians.

The work of the boards was so organized that during the examinations cases were culled out and finally acted upon by the more skilled members. The necessity of training examiners, standardizing their methods, and obtaining definite information as to the diagnostic ability of each individual became imperative. To meet this demand, Colonel Bushnell

next established diagnostic schools at Washington, Fort Benjamin Harrison, Fort Oglethorpe, and Fort Riley. Doctors were first sent to these schools and then assigned to the various examining boards. The courses in physical diagnosis lasted about three weeks, first covering signs of the normal chest, and then signs characteristic of disease. The courses involved the direct personal attention of the instructor to a very limited number of pupils. Each pupil was taken through the course step by step, and his work checked so that he either learned or failed to qualify.

Considering the need for haste and the brevity of the courses, this method of teaching gave surprising results, and one year after we entered the war 450 tuberculosis examiners were on duty. By this time the National Army had been organized, and the tuberculosis examiners had become part of large examining boards made up of cardiovascular specialists, neuropsychiatrists, orthopedists, eye, ear, nose and throat specialists, etc. The draftees were then being examined by specialists as they reported at the mobilization camps, and reëxaminations were no longer necessary. Making allowance for the difficulties under which chest examinations were made, often in thronged rooms amid more or less noise and confusion, they were well performed and many cases of tuberculosis were eliminated. No doubt many men were rejected on account of tuberculosis who did not have the disease, and likewise cases were overlooked. Colonel Bushnell, in his writings, repeatedly called attention to the "unavoidable percentage of tuberculosis" which would develop later, because, as he said, "We cannot tell whether the soldier who harbors the tubercle bacillus, as all men do, has a wide or very narrow margin of safety regarding vital resistance." That the examiner would fail occasionally was also to be expected. The tuberculosis boards examined, in all, 3,288,699 men, of whom they rejected 23,991. With reference to their work, I wish to quote Jacobs, of the National Tuberculosis Association, who, in his interesting paper on *Tuberculosis as a War Problem*, says,

> The two outstanding features in the measures taken by the United States Army for the exclusion of tuberculosis from its ranks are,—first of all, the unique and decidedly different diagnostic procedure promulgated under the direction of Colonel Bushnell; and secondly, the organization of the tuberculosis medical examiners to put into effect Colonel Bushnell's procedure. Who will deny that the exclusion of approximately 24,000 men from the army as a result of the activity of these examining boards was not in itself a very decided

factor towards improving the morale of the army, the lessening of expense, and, in general, towards winning the War?

From the very beginning of his war work, Colonel Bushnell was confronted with many intricate problems and trying situations, but he steered wisely and carried on his task without any disasters. He was a true patriot and never thought of himself while serving his country. Early in 1918 his health began to fail. The long office hours and the continuous strain without the out-of-door diversions to which he was accustomed began to tell on him. His patriotic spirit was remarkable. I believe he would have endured any amount of mental and physical suffering as long as he felt he could do some good by remaining on duty. Mistakes occurred, and wrong decisions of minor importance were made, but his general policies were always correct. It is doubtful if anyone else could have handled such a complicated war problem as tuberculosis proved to be without some mishap. Much help and valuable advice was given from nonmilitary sources. Colonel Bushnell had the backing and confidence of the medical profession, and, therefore, was strong enough to turn aside impracticable policies which were sincerely urged from time to time. He knew the practical side from the military point of view. One instance was the question of using the X-ray for the examination of all soldiers. This was strongly advocated, but rejected by Colonel Bushnell on the grounds that it was not only too expensive and time-consuming, but also fraught with many dangers. Perfectly safe in the hands of a few clinicians long experienced and skilled in its use, I shudder to think what might have happened if adopted as a routine procedure and placed in the hands of the unskilled or over-enthusiastic roentgenologist. To quote Colonel Bushnell, "Few have a conception of the physical difficulties which arise when enormous numbers are concerned—1000 plates may be handled with reasonable ease, 10,000 become difficult, and 40,000 an impossibility." Colonel Bushnell was also opposed to the view which prevailed among many tuberculosis specialists, that all cases of tuberculosis, even those with small fibrous lesions, should be excluded from the army, expressing the fear that they would break down under the stress and strain of war service. He took the stand that we must not carry the refinement of diagnosis too far, depleting the army of men who were able to serve, that the abundant food, fresh air, and healthful exercise of the soldier would strengthen, develop, and fortify, rather than break down, his resistance.

The work of the tuberculosis boards was not all smooth sailing. Need-

less to say, during the time of the reëxaminations, the boards were not always popular with Division Surgeons and Division Commanders. Soldiers were being reëxamined for everything, and it interfered with their military training and the feverish haste to mould them into fighting units. The Division Surgeon had to shoulder one more extra burden, and naturally did not always feel coöperative towards the fastidiousness of specialists. Many little difficulties had to be ironed out. Respiratory infections, especially those due to the streptococcus, began to give trouble. Colonel Bushnell was familiar with these cases, and did everything in his power to prevent errors in diagnosis, which threatened to assume large proportions at times. One tuberculosis board was discharging so many cases of tuberculosis that a neighboring city became alarmed, thinking they were going to be overrun with discharged tuberculous soldiers. A representative was sent to Washington to protest. An order was finally issued that after acceptance no soldier would be discharged from the army on account of tuberculosis unless the sputum was found positive. At least, the soldiers were first to be sent to tuberculosis hospitals for a period of observation before being discharged. A like situation had developed overseas. In the early part of 1918 something like ninety cases of tuberculosis were evacuated to the United States, and upon arrival only a small percentage were found really to have the disease. To cope with this situation, Dr. Gerald B. Webb, then a Lieutenant-Colonel in the Medical Department of the National Army, was sent to France and placed in charge of all tuberculosis work on that side. It was a fortunate selection, and no further difficulties arose. Colonel Webb soon put into effect a plan which prevented cases of tuberculosis being evacuated to the United States incorrectly diagnosed. No diagnosis of tuberculosis was permitted without a positive sputum. Negative sputum cases were diagnosed "observation, tuberculosis," and sent to certain Base Hospitals designated as "Observation Centres." Here the cases were observed and thoroughly studied by tuberculosis specialists before finally disposed of.

The location, construction and administration of all Army tuberculosis hospitals were placed in the hands of Colonel Bushnell. At the beginning of the War but one Army tuberculosis hospital existed. This was at Fort Bayard, New Mexico, with a capacity 350 beds. One year later eight Army tuberculosis hospitals were in existence, with a combined capacity of over 8,000 beds. These were located at Otisville, New York, New Haven, Connecticut, Markleton, Pennsylvania, Azalea and Waynes-

ville, North Carolina, Denver, Colorado, Fort Bayard, New Mexico, and Whipple Barracks, Arizona. The task of constructing and placing these hospitals in operation in such a short time was tremendous. While the work was distributed among many departments, Colonel Bushnell had the entire responsibility of providing hospitalization for tuberculosis patients, and seeing that the hospitals were built and ready when needed. By order of the Surgeon-General, on September 11, 1917, it was declared that disabled members of the military service would not be discharged from the service until they had attained complete recovery, or as complete recovery as was to be expected, when the nature of the disability was considered. Colonel Bushnell doubted the feasibility of this order, especially with reference to tuberculosis because, as he said, the first thought of every soldier when he found he had tuberculosis would be to go home. The order was also not in accord with those who believed that the tuberculous soldier should be treated near his home. After the armistice it was found absolutely necessary to abandon this policy, because of the overwhelming demand of the soldiers to be mustered out of the service with as little delay as possible, and the one desire to get away from military discipline.

I have given only an incomplete description of the work performed by Colonel Bushnell during the War. He attended medical meetings, prepared, read and published many papers, especially on the subject of tuberculosis as related to the War; he visited the various camps and lectured to medical officers, inspected the tuberculosis hospitals and held conferences with representative peoples on various phases of his work. He was in very poor health most of the time, and only his staunch patriotism and determination to complete the work assigned to him kept him on duty. At the annual meeting of the National Tuberculosis Association, in 1918, Colonel Bushnell was unanimously chosen Honorary Vice-President, in special recognition of his tuberculosis work during the War.

In October, 1918, my great desire to go to France led to my relief from duty in the Surgeon-General's office, and duty under Colonel Bushnell, which had lasted more than ten years. While overseas I kept in touch with him and learned of his complete breakdown in health in 1919. It was not a surprise to me. After the War was over, he returned to the retired list, and busied himself writing his book on *The Epidemiology of Tuberculosis*, and, when this was completed, began another one, *Diseases of the Chest*, written in conjunction with Dr. Joseph H. Pratt, of Boston,

which is now in press. In 1921 I had the great pleasure of seeing him again at the first meeting of the International Union Against Tuberculosis, which took place in London. He attended this meeting as chief delegate of the National Tuberculosis Association, and made a most favorable impression. After this meeting we traveled together in England and Scotland, a very pleasant and interesting experience. When I returned to the United States I visited him for a few days at his home in Bedford, Massachusetts. He was living on a small farm, leading an out-of-door life, and devoting his time to investigating certain physical signs in pulmonary tuberculosis and working on his book on *Diseases of the Chest.* He looked unusually well and seemed to have, at the age of sixty-eight, many useful and happy years before him. During the winter of 1922 and 1923, he was returned to active duty and delivered a series of lectures on Military Medicine at Harvard University. In the summer of 1923, he motored to California and there made his home in Pasadena until his death in 1924. In the spring of this year he had planned a trip east, and we were looking forward to seeing him at the Fitzsimons General Hospital. On the day of his expected arrival, a telegram was received stating that the Colonel had been taken suddenly ill, but that he hoped to be able to travel in a short time. His hopes were never realized. He was seventy-one years of age. Although he had fought tuberculosis in his own body for many years, his life span had been long. Spared a painful and lingering illness, he passed away peacefully, July 19th, 1924.

Major General John L. Hines, Chief of Staff, U. S. Army, following Colonel Bushnell's death, wrote and made a matter of official record the following commendation:

> Colonel Bushnell was a valuable and efficient medical officer wherever placed, and, in the war with Spain, he was called to service in the volunteer forces in a position above his Regular Army grade. But his outstanding ability and reputation were in connection with the establishment, management, and maintenance of general hospitals, especially those for the treatment of patients suffering from tuberculosis, in which he was an expert and authority, recognized not only in the army and in the United States, but throughout the civilized world. His death removed one to whom many are indebted for their recovery from that dread malady in the past, and whose influence will be distinctly present in the future, wherever efforts are being made to overcome its ravages.

E. H. B.

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TUBERCULOSIS IN CHILDREN

A REVIEW OF THE MORTALITY DURING THE PAST QUARTER-CENTURY IN NEW YORK CITY

GODIAS J. DROLET[1,2]

Children have been the greatest gainers from the antituberculosis campaigns in the United States. And nowhere is this reflected more strongly than in New York City, where, with a tremendous crowding of population, a definitely limited amount of space, fresh air and sunlight, and the numberless daily contacts of children with persons and premises frequently infected, there exists the widest opportunity for the tubercle bacillus to infect thousands in homes and tenements teeming with children.

Until recent times the death-rate from tuberculosis among young children, especially infants, was almost everywhere one of the highest at any period of life. In New York City, one of the earliest reports of the Metropolitan Board of Health, namely of 1868, discloses that in that year 1191 infants died per 100,000 children under one year of age. Thirty years later, in 1898, when the greater city was formed by the consolidation of the present five boroughs, the infant mortality rate from tuberculosis was already down to one-half or 609. But during the quarter of a century since the latter date, a still greater decline has taken place and in 1923 the death-rate from tuberculosis among infants was 94 per 100,000 children under one year of age, or only one-sixth of the rate of twenty-five years ago.

The antituberculosis work in America, which was inspired first by the practical demonstration of the value of the open-air life by Trudeau, was, it will be recalled, at first entirely directed to the care and treatment of those already stricken with the disease.

Sanatoria, tuberculosis hospitals and the slogan of "no uncared-for cases" were practically the limit of the first antituberculosis programmes. After that followed case-finding campaigns and the examination of

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[2] With acknowledgments to Miss L. M. Dorr for assistance with necessary compilations.

contacts. The success of various demonstrations in that direction quickly led municipal, State, public and private authorities to provide the necessary beds, at least for most of the advanced and dying cases; later, to the building of sanatoria in country places and the opening of clinics in populous centres; finally, to preventoria for children.

From the case-finding and the care-taking of the sick, the antituberculosis campaign in America has quickly spread toward the general population and the development of effective preventive measures against tuberculosis. The tremendous gain in lives saved, the constant and almost accelerating decline of the tuberculosis death-rate, especially among the young children, are proof positive of the soundness of the present programme of work with its expansion along preventive lines to include the general population. But for the sake of the record and of the recognition of the milestones in this broadening vision, it is useful to note, at least as far as a study of vital statistics on tuberculosis among children may reveal it, the mortality rates of children during the past twenty-five years in the American metropolis, where the reports of the Bureau of Records of the New York City Department of Health have been most carefully kept and show a unique picture of the progress made.

The detailed figures of the reported deaths from tuberculosis among children under fifteen years of age, each year since 1898, are shown in table 1 and the trend of the death-rate in the corresponding chart 1.

During the last twenty-six years in New York City 28,761 deaths from various forms of tuberculosis have been reported among children under fifteen years of age.

In 1898, 1,370 such deaths were registered among a total childhood population estimated at a little over one million (1,002,767). In 1923, with a child population increased by more than 675,000 (to 1,679,252), the tuberculosis deaths numbered only 547. The former death-rate of 136 per 100,000 was reduced to 33, or by 76 per cent.

In children under fifteen tuberculous meningitis causes half of the deaths, as may be seen in table 1. The death-rate from this cause in children in New York City has been reduced from 78 to 17 per 100,000, or by 78 per cent, between 1898 and 1923.

In the above group of children pulmonary tuberculosis is the next important type after the meningeal form, and nearly one-third of all of the tuberculosis deaths among children were of that form; but the death-rate, which formerly was 31, has been reduced to 10, or by 68 per cent. Pulmonary tuberculosis in children, though it has also greatly declined

in New York City, has not been reduced quite as fast as the other forms. The constantly increasing population of this metropolitan area and the greater opportunities for infection, especially through the respiratory tract, may be in part the cause for this.

TABLE 1

Tuberculosis mortality among children under fifteen

New York City, 1898 to 1923*

YEAR	MENINGITIS		PULMONARY		ABDOMINAL		OTHER FORMS†		ALL FORMS	
	Deaths	Rate‡	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
1898	786	78	307	31	54	5	223	22	1,370	136
1899	766	74	362	35	40	4	233	23	1,401	136
1900	803	76	316	30	43	4	206	20	1,368	130
1901	675	62	290	26	89	8	137	13	1,191	109
1902	722	64	239	21	78	7	125	11	1,164	103
1903	720	62	259	22	94	8	82	7	1,155	99
1904	663	58	328	28	92	8	95	8	1,178	102
1905	568	48	332	28	75	6	105	9	1,080	91
1906	665	54	350	28	82	7	100	8	1,197	97
1907	664	54	345	28	76	6	88	7	1,173	95
1908	691	54	327	26	86	7	96	7	1,200	94
1909	716	54	364	27	76	6	101	8	1,257	95
1910	688	50	271	20	85	6	155	11	1,199	87
1911	764	55	335	24	74	5	156	11	1,329	95
1912	681	48	287	20	94	7	160	11	1,222	86
1913	694	48	353	25	77	5	164	11	1,288	89
1914	630	43	321	22	65	4	150	10	1,166	79
1915	649	44	324	22	50	3	177	12	1,200	81
1916	568	37	256	17	44	3	135	9	1,003	66
1917	571	37	272	18	42	3	198	13	1,083	71
1918	615	40	314	20	49	3	128	8	1,106	71
1919	479	31	271	17	49	3	115	7	914	58
1920	395	25	241	15	45	3	95	6	776	49
1921	298	18	168	10	34	2	74	5	574	35
1922	320	19	195	12	23	1	82	5	620	37
1923	277	17	162	10	22	1	86	5	547	33

* Compiled from Reports New York City Department of Health by G. J. Drolet, Statistician, New York Tuberculosis Association.

† Includes acute miliary tuberculosis, Pott's disease, white swelling, scrofula and general tuberculosis.

‡ Death rate per 100,000 children under fifteen years of age.

Note: The number of children under fifteen in New York City in 1898 was 1,002,767; and, in 1923, it was estimated at 1,679,252.

The abdominal type of tuberculosis in children under fifteen in New York City, though never causing a large proportion of the deaths, as

already noticed by other observers in America in contradistinction to this form of tuberculosis especially in Great Britain, shows the greatest decline here. Until recently the death-rate from tuberculous peritonitis frequently reached 7 and 8 per 100,000, whereas in the last couple of years it has gone down to one. Undoubtedly, the continued and unique measures which the health authorities of New York City have adopted, first, of complete pasteurization of all milk except the certified, and second, by the annual examination of almost 100,000 food handlers, must be given the greater share of credit in the gains against this form of tuberculosis, largely due to infection from food supplies.

DECLINE GREATER IN CHILDREN THAN IN ADULTS

In 1898 all the deaths from the various forms of tuberculosis in New York City, both among children and adults, numbered 9,265 and those of children under fifteen 1,370, or 15 per cent of the total. In 1923, with 5,673 deaths at all ages, only 547 or 9.6 per cent were among children.

During the quarter of a century between 1898 and 1923, the number of tuberculosis deaths among adults in New York City over fifteen years of age decreased from 7,895 to 5,126, or by 35 per cent, while among children under fifteen the number of deaths fell from 1,370 to 547 or by 60 per cent, although the population of the city doubled to six millions during that period.

If the death-rates from tuberculosis among children in New York City are compared against those for the entire United States registration area, which includes, of course, the large populations more favorably located in rural sections, the following differences are noted: In 1900 the death-rate from tuberculosis among children under fifteen in the United States registration area was 64 per 100,000; in New York City it was 130, or more than twice as high. In 1921 the death-rate in that age group in the United States area was 28; in New York City it was down to 35, the handicap having been reduced from an excess rate of 103 per cent to one of 25 per cent.

TUBERCULOSIS AMONG INFANTS

Infants remain, of course, the most susceptible of all children to tuberculosis, but the increasing effect of the more or less general segregation of advanced cases of tuberculosis in New York City, the systematic disinfection, cleaning and renovation of the former homes of consumptives

by the Health Department for years, the pasteurization of the milk supply, the examination now of food handlers, all have cumulated in giving the young child an opportunity to develop with a much greater freedom from massive and too frequent infections with the tubercle

TABLE 2

Tuberculosis mortality among infants

New York City, 1898 to 1923

YEAR	MENINGITIS		PULMONARY		ABDOMINAL		OTHER FORMS		ALL FORMS	
	Deaths	Rate*	Deaths	Rate*	Deaths	Rate*	Deaths	Rate*	Deaths	Rate*
1898	291	353	69	84	41	50	101	122	502	609
1899	281	332	98	116	34	40	79	94	492	582
1900	301	347	66	76	31	36	80	92	478	551
1901	246	275	64	71	52	58	33	37	395	441
1902	236	256	47	51	42	45	23	25	348	377
1903	249	261	40	42	42	44	22	23	353	370
1904	211	223	61	65	33	35	17	18	322	341
1905	154	148	65	63	33	32	17	16	269	259
1906	197	176	64	57	39	35	23	21	323	289
1907	193	160	64	53	35	29	24	20	316	262
1908	181	143	56	44	33	26	19	15	289	228
1909	182	148	85	69	24	20	20	16	311	253
1910	166	128	53	41	37	29	36	28	292	226
1911	198	147	51	38	24	18	42	31	315	234
1912	173	127	43	32	39	29	36	27	291	215
1913	169	125	40	30	27	20	42	31	278	206
1914	155	110	40	28	8	6	36	26	239	170
1915	171	121	46	33	10	7	51	36	278	197
1916	153	111	42	31	11	8	39	28	245	178
1917	130	92	37	26	9	6	53	38	229	162
1918	151	110	42	30	10	7	36	26	239	173
1919	107	82	47	36	14	11	26	20	194	149
1920	77	58	46	34	14	11	19	14	156	117
1921	88	66	39	29	7	5	21	16	155	116
1922	69	53	31	24	4	3	29	22	133	102
1923	66	51	28	22	7	5	21	16	122	94

* The rates from 1898 to 1904, inclusive, are per 100,000 children under one year as determined from the Census; thereafter, each 100,000 births reported.

Note: In 1898, the number of infants less than a year old was estimated at 82,453, whereas in 1923 it was 129,160.

bacillus. The annual figures since 1898 of tuberculosis mortality among infants may be studied in table 2.

In 1898, 37 per cent, or more than one-third of all the tuberculosis deaths in children under fifteen, occurred among infants, 502 such deaths

having been noted out of a total of 1,370. In 1923, 22 per cent, or a little more than one-fifth of the tuberculosis deaths in children occurred among infants, namely, 122 out of 547.

It is to be noted that during that period the annual number of infants under one year of age in the total population increased from 82,000 to 129,000. The death-rate from various forms of tuberculosis among infants in 1898 was 609 per 100,000 children. In 1923 it was reduced to 94 or by 85 per cent.

The greatest number of tuberculosis deaths among infants is, as is well known, of the meningeal type, but the rate from that cause in 1923 was only one-seventh of what it was twenty-six years ago, when it was 353 per 100,000 as compared with 51 last year.

The pulmonary type of tuberculosis among infants accounts for about one-fourth of the tuberculosis deaths in that group; formerly the proportion was one in seven of the total deaths from that cause among infants. Probably the greater declines in the meningeal, and especially the abdominal forms, are responsible for the different proportion of the pulmonary type to the total, but even then the death-rate of pulmonary tuberculosis among infants has fallen from 84 to 22, or by 74 per cent.

The abdominal forms of tuberculosis, which formerly among infants were reported in one out of every twelve tuberculosis deaths among them, are now only one in eighteen, and the mortality from that cause has been practically wiped out, the deaths having been reduced by 90 per cent, or from 50 to 5 per 100,000. Here, undoubtedly, is to be found the greatest effect of milk pasteurization and the continuous campaigns for cleanliness of the food supply of New York City.

After tuberculosis of the central nervous, respiratory and alimentary systems, the other forms of the disease among infants are mostly of the bones and joints. In New York City one-fifth of all tuberculosis deaths among infants were of that type in 1898, when the rate was 122 per 100,000. In 1923 they were one-sixth, and the death-rate from that type of tuberculosis had declined to 16, or by 84 per cent. Tuberculous cripples, hunchbacks, and children with necks scarred from adenitis are becoming a relative rarity in New York City.

TUBERCULOUS INFECTION OF INFANTS: ITS SERIOUSNESS

Up to recently it was feared that the infection of infants with tuberculosis would almost invariably result fatally. While this might be true

where babies were daily exposed to repeated and continued massive infections with tubercle bacilli, under ordinary conditions of life at present in New York City the facts available do not bear out this assumption. More than 130,000 births occur here annually. The lowest percentage of tuberculin reactions in children under one year of age, from various surveys, rarely ranges lower than 10 to 12 per cent, with greater proportions in congested parts of the city. The author found it to rise to 25 per cent among certain populations on the East side a few years ago.[3] This would indicate that there are, at the minimum figure, 13,000 children under one year old in New York City who are already infected with the tubercle bacillus. And yet the total number of deaths from all forms of tuberculosis in infants reported in 1923 was only 122. Granting the difficulty of diagnosis of tuberculosis in many infants dying apparently from other causes and that the number was, let us say, ten times greater than that reported, it would give only 1,220 tuberculosis deaths out of 13,000 infected. In fact, the total deaths of all infants from every cause of mortality numbered only 8,578 in New York City in 1923. This would show, therefore, that ordinarily the majority of infants infected with tuberculosis survive.

The general tuberculization of the populations in cities, beginning early in childhood, and the, after all, quite limited proportion of those finally dying from the disease should long ago have made us realize that this survival of great numbers of children infected under ordinary conditions of life was daily taking place.

DIFFERENCES IN SEX AND AGE GROUPS

Tuberculosis among children is a very frequent cause of mortality, as already noted especially among very young ones. But between the ages of five and fifteen, the golden age of childhood as far as mortality

[3] A recent investigation of the incidence of tuberculosis in babies under two years of age, now being made under the direction of Dr. M. Alice Assersen of the Children's Service of the New York Tuberculosis Association, would seem to indicate that, while the percentage of infection prevailing at present in New York City is still as high as 10 per cent in very young children coming under the observation of tuberculosis clinics, hospitals and other institutions for the care of children,—all catering more to the sick than to the well,—the percentage of infected babies among more normal healthy groups, such as those at the baby welfare stations and health centres, is found to be much lower, indicating that in the general and normal child population tuberculous infection is probably now less frequent than has usually been thought to be the case.

from any cause is concerned, the tuberculosis rates are lowest. Marked differences, as shown in table 3, occur, however, in each sex.

In young children under five the tuberculosis death rate each year in New York City is practically always higher among boys than among

TABLE 3

Rate of mortality in children

From all forms of tuberculosis in each sex per 100,000 living at each five year age group, New York City

YEAR	UNDER FIVE			FIVE TO NINE			TEN TO FOURTEEN		
	Boys	Girls	Both sexes	Boys	Girls	Both sexes	Boys	Girls	Both sexes
1898	**315**	265	290	**47**	43	45	29	**56**	42
1899	**301**	271	286	45	**47**	46	33	**56**	45
1900	**305**	234	269	**48**	44	46	33	**53**	43
1901	**244**	189	217	**49**	38	43	28	**64**	46
1902	**217**	194	206	44	**49**	47	28	**45**	36
1903	**201**	182	191	**50**	40	45	30	**57**	44
1904	**206**	173	190	50	**53**	51	37	**57**	47
1905	**181**	162	171	42	**46**	44	28	**51**	40
1906	**207**	162	185	38	**43**	41	36	**60**	48
1907	**195**	168	181	**49**	41	45	28	**57**	42
1908	**193**	150	172	45	**52**	48	33	**60**	47
1909	**215**	157	186	38	**44**	41	31	**51**	41
1910	**182**	158	170	41	**47**	44	20	**47**	34
1911	**186**	175	181	**47**	42	45	40	**49**	45
1912	**176**	151	164	**47**	42	44	27	**44**	36
1913	167	**171**	169	43	**45**	44	27	**52**	40
1914	**161**	124	143	44	**55**	50	32	**44**	38
1915	**162**	147	155	38	**43**	40	22	**51**	36
1916	**134**	114	124	**34**	31	33	24	**45**	35
1917	**148**	127	138	**36**	34	35	26	**42**	34
1918	**140**	124	132	29	**34**	32	28	**63**	45
1919	**118**	92	105	**34**	27	30	26	**42**	34
1920	**89**	85	87	**28**	24	26	20	**36**	28
1921	65	**67**	66	13	**17**	15	15	**30**	22
1922	**87**	58	73	16	**17**	16	15	**26**	20
1923	**66**	59	62	13	**14**	13	12	**27**	20

Note: Bold figures indicate a higher rate than that of the opposite sex.

girls. In 1898 the tuberculosis death-rate in that group was 265 among 100,000 girls, and 315 for boys. In 1923 it was 59 for the former and 66 for the latter. But between the ages of five and ten the tuberculosis rate oscillates between girls and boys, and in fact is generally about the same in both.

Among girls between ten and fifteen years of age tuberculosis is steadily a more frequent cause of death than among boys, in fact almost twice as great. The greater strain attendant to the development of puberty must, of course, be responsible among the girls and once more, at least in approaching adult life, we see the common result of tuberculosis hatching out whenever too great a strain is put upon certain individuals' resistance. Preventive work against tuberculosis should, therefore, concentrate to a greater degree upon girls of that age than upon boys. The latter, on the other hand, will reach a period of greater stress when they go out to work or enter industry a few years later when, again, measures should be particularly directed on the behalf of young men and young women, who are obliged to leave the shelter of the home and who are as yet unaccustomed to the change and to the greater requirements of adult life.

PRINCIPAL CAUSES FOR THE DECLINE IN NEW YORK CITY

To the causes already mentioned as partly responsible for the great decline of tuberculosis in children in New York City some further details should be added. First, we would draw attention in chart 2 to variations noticeable at different times during the period of 1898 to 1923. Between 1898 and 1905 a great fall in the tuberculosis death-rate in children took place, when the rate fell from 136 to 91; but between 1905 and 1911 an almost stationary or level period occurred and the rate oscillated between 91 and 95.

A second period of decline in the tuberculosis death rate of children in New York City set in from 1911 down to 1916, when the rate fell from 95 to 66. The fall was interrupted during the war and probably by the influenza epidemic in 1917 and 1918. Beginning with 1919 and continuing down to 1923, the decline in tuberculosis continued and the rate among children fell from 71 to 33.

The segregation of advanced cases especially, often a costly and apparently discouraging work because of the many deaths taking place among them, has accomplished more than merely assuring devoted and scientific care of the seriously ill. It must be conceded to be the prime factor in contributing to the reduction of tuberculosis in children, as well as saving the lives of their parents occasionally.

The writer has at hand figures of the total number of patients in institutions, both hospitals and sanatoria, in New York City since 1907 and

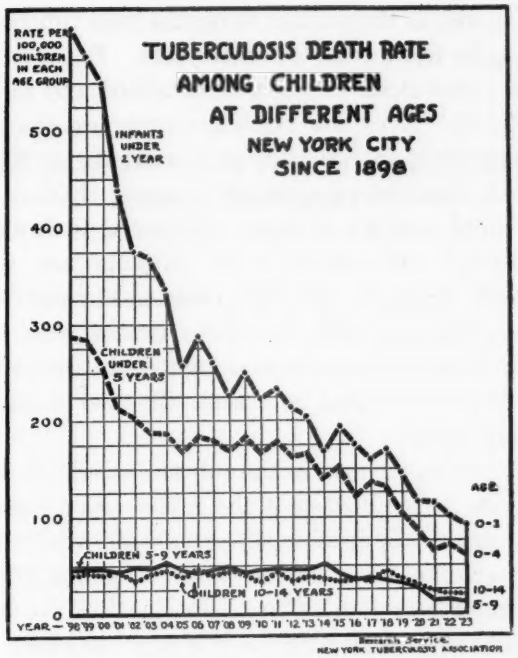

CHART 1.

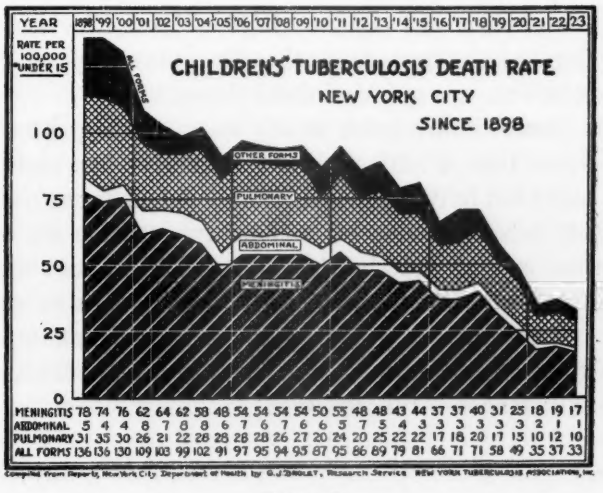

CHART 2.

subsequently, as well as the number of deaths from tuberculous meningitis in children under five during the same years. Between 1907 and 1916 the number of tuberculosis patients hospitalized and in sanatoria rose from 3,300 to 9,549. Even now there are rarely less than 7,000 cases of tuberculosis segregated in hospitals and sanatoria of New York City. The deaths from tuberculous meningitis among children in New York City and the total number of cases segregated in institutions are in obvious correlation. Whenever more patients are segregated the meningitis deaths decrease, and *vice versa* if the number is reduced. More recently, of course, with the fewer deaths from tuberculosis in New York City there are fewer beds occupied but the continued plan of hospitalizing all the advanced or acutely ill cases possible has been a sound life-saving policy.

Second, to return to changes in the tuberculosis death-rate of children at different times, it is noted that the rates, which between 1906 and 1913 remained practically level at 48 per 100,000 without further drop, coincided with a period when no new tuberculosis institution was added to the resources of New York City. But in 1913 the large municipal hospital at Sea View with 763 beds was opened; and then again, but not until then, the meningitis death-rate in children broke. In 1914 the private hospital of St. Anthony's was also added to the public resources, with more than 200 beds at that time. The same year, also, the general pasteurization of milk was required in New York City and the tuberculosis death-rate from forms other than the pulmonary, which is largely confined to children, was quickly halved thereafter.

Children, therefore, are being wisely spared in a greater proportion than ever before from infection with tuberculosis when their bodies and organs are as yet not fully developed. And, with an increasing amount of work in their behalf in open air and many nutrition classes, through other countless ways devised by the child welfare sections of private and public organizations, with the teaching of health habits to build up their resistance and natural strength, they are being given an opportunity to reach a useful manhood and womanhood with a real chance of escaping altogether the ravages of tuberculosis.

HUMAN RESISTANCE TO TUBERCULOSIS AT VARIOUS AGES OF LIFE[1]

ALLEN K. KRAUSE

Through an established tuberculous infection a human being gains in resistance to all exposures to reinfection, from within or without, that he may undergo. He continues to enjoy some measure of increased resistance as long as the original infection persists. Observations on the behavior of tuberculous animals toward artificial reinfection permit no other conclusion.

Presumably, most of mankind, in the natural course of events, receive as first infections tubercle bacilli of quantity and virulence that they can hold in check or completely overcome. Presumably, too, all such relatively ineffective bacilli arouse the body to anatomic change of some degree. There certainly take place first infections which through the reproduction of countless generations of descendant bacilli hold throughout the term of an ordinary life, yet never transgress the bounds of clinical nonactivity. There no doubt are also occurring numerous first infections of limited duration; set up by few germs, they disappear, and leave the body again tubercle-free. By far the greater number of us experience one or the other of these types of first infection.

Those first infections that sooner or later make themselves felt, as processes that become progressive or have got beyond control are, of course, only a fraction of all first infections. What part they make of all cases of active tuberculosis cannot be told; any estimates of the proportion of illness that is due to the germ stock of "original settlers" must at present be no more than guesswork; that the ratio is considerable is all that we may say with any approach to precision.

But, whatever be the type of tuberculous infection that resides within a man, his individual resistance is increased by it. If his maximum tolerance before infection was, say, ten tubercle bacilli, infection has made this ten plus, whether the new infection come from the outside world or proceed from a focus within the body. There is the best of

[1] From the Kenneth Dows Tuberculosis Research Fund of the Medical Clinic of the Johns Hopkins Hospital and University.

evidence that this increased resistance is expressed in two ways: (1) it will ward off more bacilli in such a manner that anatomic response to them is absent or is so slight that no new infection can be said to result, and (2) it will give rise to a type of anatomic (and biological?) response which will tend to fix bacilli *in situ* or limit markedly the spread of large numbers of bacilli.[2] In the first instance it kills off bacilli that would be sufficient to infect a nontuberculous person, and no reinfection of any kind results. In the second case it prevents or retards progression of the reinfection, and thus makes an adequate number of germs set up a more benign and favorable process than they would cause as a first infection: as it happens, such processes are comparatively limited and chronic if bacilli remain alive.

It is quite important to know that the specific immunity derived from first tuberculous infection prevents reinfection. Within certain limits of "dosage" of bacilli it will do this. But much more important is the additional fact, none too well appreciated, that in the so called immune animal of experiment some type of anatomic change usually follows reinfection.[3] In other words, lesion results, and the numbers of reinfecting bacilli do not have to be particularly large to produce it. The point is that, compared with the evolution after first infection, the lesion is modified. In its origin it tends to confine the bacilli and it takes a more chronic course.

Biological experiment would further suggest the occurrence of two other events in the immune, that is, the infected human being: (1) the eventually thorough healing of foci of reinfection which were produced by bacilli that would be of sufficient virulence and number to cause permanent infection as first infections, and (2) the development of foci of reinfection of prolonged duration and capable of bringing about symp-

[2] See Appendix A: *Remarks on Conditions Necessary to Arouse the Allergic State and on Immunity through the Fixation of Bacteria.*

[3] As evidence of Trudeau's high scientific attainments we may quote from his *Artificial Immunity in Experimental Tuberculosis* (*New York, M. J.*, July 18, 1903): "Behring seems to have produced in calves an immunity which is so perfect that the tissues fail to react to the virulent inoculation by the formation of tubercle, and no trace of it is left on (*sic*) the lungs of his protected calves. In my experience with small animals, the degree of immunity I have succeeded in obtaining does not prevent the local reaction of the tissues to the virulent inoculation." Again, in the same paper: "You will notice that, in the lungs, as is the case in the eye the virulent inoculation produces in the tissues of protected animals at first even a more marked reaction than in the controls, so much so as to gain the impression that the protected are more susceptible than the controls." To-day we can say with surety that, in members of species susceptible to tuberculosis, immunity can be manifested only through tissue reaction (that is, lesion), if dosage is more than minimal.

toms and disability, that is, active tuberculosis.[4] The issue of reinfection of the immune person will turn, first, on the numbers of living bacilli concerned at any one time, on the frequency of their reception or their transference from point to point in the tissues, and on the time that intervenes between successive infections (including metastases). Of considerable moment will also be the place of localization of every particular reinfection; for instance, the result will vary as this is a lymph node, the pleura, or the pulmonary tissue at the hilum. In autogenic reinfection the place of origin and the avenue of transport from it will be factors of importance; the eruption of a focus in a tracheobronchial lymph node is likely to cause tuberculous pneumonia, while that of an identical process in the retroperitoneal lymph nodes may provide the setting for generalized miliary tuberculosis. As they make their way to the surface, similar foci in cervical lymph nodes would discharge to the outside, and give rise to relatively benign illness. In general, the lung's natural avenues of dissemination make ulcerative pulmonary tubercle more momentous than comparable processes in other organs, inasmuch as they involve the possibility of easy and direct reinfection of the other lung, of the upper respiratory tract (larynx), and of the digestive tract.

In addition to all this, the prime factor of constitutional and organic condition, of physiological equilibrium and derangement, is always at work; and this varies continually with changing environment and experience—with sickness and health, with stress and repose of body and mind, with atmospheric temperature, humidity and movement, with deprivation and repletion.

It so happens that among our older civilizations a number of people that increases continually from birth to adult age receive in the ordinary course of affairs tuberculous infections. These are of such a kind that fully three-fourths and more of the infected are never made ill thereby. It must result, then, that the larger part of mankind is given greater resistance to tuberculous infection and its further extension than it enjoyed at birth, that this resistance is increased within the span of individual lives and that, between birth and maturity, the number of more resistant persons is, actually and relatively, greater at any given age than for earlier years. It is beyond dispute that, *with everything else equal,* the two natural circumstances of immunity through infection and

[4] See Appendix B: *Remarks on the Healing as well as on the Long Continuance of Foci of Reinfection.*

of mounting incidence of infection with advancing age combine to make more persons of twenty years more resistant to tuberculous infection than at age fifteen, more at fifteen than at ten, more at ten than at five, and so on. Or, to put the case in another way—in the way that it is generally expressed—the adult is more resistant to tuberculosis than the child. If the latter generalization is meant to embody anything more than the numerical relations mentioned, it does so inaccurately and at the risk of arousing a false impression—until it can be shown that, for some other reason, the *infected* adult is more resistant than the *infected* child or the *noninfected* adult more resistant than the *noninfected* child. At the same time there is no evidence to show that the *noninfected* adult is *specifically* more resistant than the *infected* child, while the established facts of resistance suggest the opposite relation; namely, that *infected* children may not be as susceptible to tuberculosis as *noninfected* adults. We must keep straight, then, that as concerns *specific immunity* the situation is that more adults than children have an increased resistance to tuberculosis and that many children are no doubt more resistant to it than a fair proportion of adults—fifty per cent of infected children, let us say, as against twenty per cent of noninfected adults. As a class adults are more resistant than children because there are more infected adults than infected children; as individuals they need not be.

Indeed, if we apply to the situation among human beings the knowledge gained from pathological observation and experimentation on animals and from the practice of cattle immunization, this would indicate that, in general, infected children are likely to have, or should have, a greater resistance than infected adults. If we assume, as not a few do, that the ordinary childhood infection lasts into adult life, we also usually take for granted further that such early infections are sufficient to protect against the common exposures of later childhood and adolescence and that, accordingly, no reinfections result from the latter. We find by experiment that an animal's immunity decreases as its infection wanes; just as we learned from our attempts to immunize cattle with living bacilli that after several years a highly increased resistance is wont to fall markedly and even vanish,—a circumstance that we have attributed to the lapsing of the several artificial infections of immunization.

Closer observations of infected animals and the enormously extended practice of roentgenography have also given us an almost new perception of the healing and disappearance of tubercle in both the laboratory animal and man. Healing, obliteration and sterilization of processes

are common: there can no longer be any dispute on this point. (See Gardner (1), Krause (2), Amberson (3), Krause (4).)

We would assume, then, that as time goes on the mild infections of childhood would tend to regress and, in many instances, heal. All such closing in of infection and encroachment upon it would necessarily carry with it a decline of specific resistance by just so much; and, after the evolution of infection has reached its acme in the individual child, the tendency would afterward be toward retreat and, *unless immunity were again whipped up by new infections from without or new extensions of already present infection,* a child should have less resistance five or ten years after first infection than a year after it.

In 1919 I reported in great detail the history of a case of tuberculosis in an Italian boy,[5] then fourteen years old, who had been under continuous observation at our Dispensary since 1909, when he was not quite four years old. He had had manifest tuberculosis in many places, including the ulna, the tibia, the first rib, and the inguinal, cubital, axillary, cervical and abdominal lymph nodes. He had also had tuberculous peritonitis and phlyctenular conjunctivitis. Physical examination and the X-ray had disclosed a gradual accretion, and then subsidence, of pulmonary infection, although symptoms of pulmonary disease (activity) never developed. During a period of seven years (from 1909 to 1916), in which he was continually ill, the boy had undergone several surgical operations for his bone and lymph-node tuberculosis. He was at one time (in 1910) so sensitive to tuberculin that he would react violently (puncture reaction) to 1/100,000 mgm. of O.T. given subcutaneously, while 4/100,000 mgm. would bring on a marked focal reaction.

In my account of 1919 I mentioned that, beginning with 1917, the boy failed to react to the Pirquet test, and had remained negative to this test up to the time of my report. As it happened, he first achieved a clinical arrest of his disease in 1917 after a stay at the Maryland State Sanatorium, when, for the first time since late infancy, his tuberculosis could be called inactive.

This boy has now become a young man of twenty. I see him once a year, when he is thoroughly examined, roentgenographs of his chest are taken, and skin tests (Pirquet) made. *For eight successive years (since 1918) he has remained negative to the Pirquet test.* Needless to say, also,

[5] *A Case of Multiple Tuberculosis in Childhood, Medical Clinics of North America,* W. B. Saunders Company, Phila. & London, May, 1919, pp. 1781–1815.

he has kept in perfect health and worked (as a clothes-presser) without interruption. Except for the old scars of his numerous operations *he presents no evidences of tuberculosis anywhere.*

Here then is a positive and unusually well-documented case, the implications of which may merit discussion. We have an unusually prolonged and extensive case of tuberculosis, one that continues uninterruptedly throughout childhood, that in a clinical sense heals completely with the approach of adolescence (though the latter was delayed in the particular case). At the same time a hypersensitiveness, which was once extreme, fades until it vanishes to a point at which it will not respond to the test used ordinarily to disclose it and usually applied also to elicit our modern information on the incidence of infection. If one may judge from the common run of studies, our patient, if tested to-day in the usual way and without knowlege of his history, would be set down by many observers as an individual who had escaped infection, and he would no doubt furnish another addition to the category of the noninfected.

The conclusion is compelling that if such extensive infection can be done away with and such great hypersensitiveness can vanish, the more ordinary condition of less or slight infection and hypersensitiveness is frequently disappearing. Several years ago I wrote (5):

> Estimates, then, of what proportion of adults fall ill from post-puerile infection and what ratio from childhood exposure are usually founded on bias and imagination. We have no way of accumulating the evidence that will give them scientific weight. No one has yet kept careful records from infancy to and through adolescence, of the ups and downs, the appearance, disappearance and reappearance, of the Pirquet reaction, that index to infection, in only ten of the millions of infected children. It may be that for longer or shorter periods we would find that a large proportion would exhibit nonreactivity, and therefore noninfection, where reaction and infection had been shown before; and further that many of these would later again give the test of infection,—in their case, reinfection. What little has been done in the way of prolonged and continued observation of the individual child's response to infection tests—and it is little enough—has been concerned with clinic children, most of whom were under observation for an infection which had become so well established, had developed to such a point, that illness or abnormality was noticeable; and we must admit that the possibilities of the subsequent course of infection in these children would be quite different from those of the very slight and presumably transient infections that might follow the almost negligible exposures which many others experienced.

Except for a study by Austrian (6), based on observations made at our own Dispensary, the present state of our exact information on this important matter is not much different from what it was three years ago. Data derived from tests on members of varying groups of children continue to appear and, being the resultant of only single observations on individual subjects, they add little to our well-established knowledge that there is an increasing incidence of human infection from birth to maturity. The more difficult, more protracted, and far more important studies, which will trace the course and fate of known infections throughout the years of childhood, are still to be made; and it may be predicted that they will be fruitful enough in new information and concepts to repay the extraordinary pains and time that must be devoted to them.

Although Austrian's material cannot be considered sufficient to warrant much in the way of broad conclusions, it yielded results that were positive enough to be of significance and to point toward the probabilities of the case. He found, for instance, that when 97 children, who had reacted positively to Pirquet tests in 1915–1916, were retested in 1920, ten, or 10.31 per cent of them, now reacted negatively (at the same time 15 children who had reacted negatively in 1915–1916 had become positive reactors in 1920). In 1923 seven of the 10 negative reactors of 1920, who had been positive in 1915–1916, still remained negative. Austrian is quite moderate in believing that his findings suggest "the validity of the hypothesis that infection may vary in degree from time to time and may even die out," and that "a positive reaction does not foretell what will be the course of the infection nor does it indicate whether the infection is an initial one or not."

We might suppose that, in the case of the Italian boy who has been kept under observation for sixteen years, the infection was a bovine one and that it died out because it was due to germs of relatively low virulence. Personally, I am inclined to believe that it was of bovine origin. But, if such were the case, and if Park and Krumwiede's old figures[6] are representative of conditions in communities which use unpasteurized cow's milk, it would emphasize the probability that roughly one-quarter of those children who are infected before six years of age gradually lose their infection and reactivity with the advancing years of childhood. And, if all our experimental work and the innumerable

[6] From birth to 6 years, human-bacillus infection 73.5 per cent, bovine-bacillus 26.5 per cent; from 6 to 16 years, human-bacillus 75 per cent, bovine-bacillus 25 per cent; over 16 years, human-bacillus 98.7 per cent, bovine-bacillus 1.3 per cent.

observations on immunized calves are worth anything, it is as certain as can be that this bovine-infected quarter of our infected children slowly yield up their specific immunity with the years. There is, moreover, every reason to believe that a large number of children who experience human-bacillus infections undergo a similar diminution of specific immunity.

As a matter of fact and clinical experience childhood is, of all ages, the most spared from the ravages of tuberculosis. From three to twelve and fifteen years of age the number of infected persons is continually increasing, which proves that the external opportunities for infection are numerous and ripe in these years; yet, paradoxically, manifestations of clinical illness from tuberculosis are relatively mild and deaths from tuberculosis are much fewer, in proportion to the number of infected persons, than at any other period before or after. Both morbidity and mortality of adult tuberculosis are many times greater than those for childhood (excluding infants).

If the data of infection could be obtained, we would hazard the estimate that, *in proportion to the number of infected*, the death-rate from tuberculosis at age 40 is at least five times as great as that at ages 5 to 12. As a matter of fact, between 1915 and 1920 the mortality rate for males at ages 40 to 60 in New York City was about 450 per 100,000 and for those at ages 5 to 12 about 50 per 100,000. A conservative estimate of the number of infected males at the upper ages would be 75 per cent, or 75,000 per 100,000, and for the lower ages 40 per cent, or 40,000 per 100,000. If such an approximation were granted we would calculate the deaths in the former group as being 450 per 75,000 infected, or roughly 1 death for every 170 infections, while in childhood there would be 50 deaths for every 40,000 infected, or 1 death for every 800 infections.

It has been customary to ascribe this favored situation of the child to environmental differences. Stress, so the explanation runs, is a powerful determinant of active tuberculosis, and of this the adult suffers much and the child relatively little. The difference between the adult, tapping his reserves, and the child, sparing his and adding to them, is reflected in more and graver tuberculosis among mature people.

We would not minimize this influence of overstrain; it is, we believe, the most potent immediate contributing factor in the origin and development of active tuberculosis. On the other hand, we cannot be blind to the common observation that childhood is a period of much ill health,—

of malnutrition and anaemia, of several years of a succession of characteristic acute infections, of acute and chronic disturbance of the upper and lower respiratory tracts, of faulty hygiene and general disregard of healthful living. In these respects the generality of adults are certainly as favorably circumstanced as children,—more so, we believe; and, with everything else equal, we should expect the contributory factors of childhood to bring about a more even balance with adult tuberculosis than actually exists.

Be all this as it may, there remains some warrant for attributing the low morbidity and mortality of tuberculosis in childhood to two factors other than environmental: (1) to a smaller number of individuals with infection, which means that there are fewer to become actively tuberculous and (2) to a higher resistance of those who are infected. The first contingency is selfevident: we would look for fewer cases of illness to develop out of a population that was half infected than in one three-quarters or five-sixths infected. But, while this might help to explain a slighter case incidence, it would throw little light on the milder character of the illness that ordinarily develops. Both low incidence and slight mortality become comprehensible if we imagine that *infected* children have, in general, a high grade of specific immunity. In the very nature of things their infection must be relatively recent: we need not and may not speculate, as for adults, that it was received years and decades before. Being recent, it still keeps up as competent an immunity as can exist without progressive infections; just as it makes young calves markedly resistant for the first couple of years after artificial, immunizing infection. We would venture, as worthy of consideration, the suggestion that the case and death-rates of adults are so markedly greater than those of children *partly* because, with the lapse of time since early infection, this has faded and the immunity of many has therefore become progressively less since earlier in life. Such a concept would, of course, allow for more adult reinfection than some writers are willing to admit. Nevertheless, it is given for what it is worth and with an effort to bring into accord many conflicting facts of epidemiology, clinical tuberculosis at all ages and experimental tuberculosis.

The following additional observation may be allowed here: Discrete childhood pulmonary tuberculosis (active) originates typically at the hilum; that of adults more toward the periphery of the lung and near the summit. Unless one entertains the thoroughly improbable idea that the transmission of pulmonary infection between childhood and maturity

is normally by retrograde lymphatic *conveyance*, one cannot, at the same time, hold two such contradictory views as that adult pulmonary tuberculosis arises, in most cases, out of childhood infection and that adult pulmonary tuberculosis is, in most cases, acquired by inhalation. If the average adult cannot be or is not reinfected from without, then his ordinarily mild apical infection must arise haematogenously. If he inhale it, it must be a reinfection. Attention to all the known facts, rather than too exclusive adherence to a point of view, would suggest that the usual sluggish apical process represents often a late reinfection on soil made resistant by anterior infection and that its commonly chronic, fibrous and circumscribed evolution is, no doubt, an expression of an immune state existing when the reinfection was received.

Viewed in its entirety, resistance to tuberculosis is a complex property, made up of several or many bodily elements. It surely includes more than whatever grade of specific immunity is acquired through infection; and we should fall into error were we to classify the individuals of susceptible species as resistant or nonresistant *only* according as they were infected or noninfected. Individual differences of resistance that rest upon inherited constitutional qualities, which vary with individuals or groups of individuals, are peculiarly intangible and elusive of definition; but we must assume their reality, because in a broad way there is no little evidence to indicate it. Yet, if the several ages of man are characterized by definite group differences in resistance, it would be impossible to conceive how inherited qualities contribute to a result that would make adults more resistant than the young. An inherited increased resistance should make itself felt in infancy, in childhood, in youth and in old age; that is, if it is an inherent tissue attribute, not dependent on those normal changes of structure and function that proceed throughout life. If, therefore, it is at work it can hardly create a general condition of increasing resistance with advancing age, or contribute to it. Indeed, if we were to assume the possibility of an inherited resistance that changed with age, it would surely be more natural to suppose that with the passing of years after birth the quality transmitted by inheritance was likely to grow weaker,—that the adult would therefore have less of an inherited resistance than the child.

But it is a fair speculation that with increasing age it is a natural habit of the body to undergo certain anatomic and (or) physiological changes of a kind that render it more resistant to tuberculosis. If this could be

shown it would put beyond question the view that adults are so constituted that, with everything else equal, they withstand tuberculous infection better than the young.

One might suppose, for instance, that the profound changes of puberty normally exerted, in some way, an action on the body so that the tissues would put up a better defense against infection. Indeed, Lawrason Brown has hazarded some such view to account for the *apparently* abrupt falling off of bovine-bacillus infection in human beings after age sixteen: he suggests (7) "that at puberty certain changes might occur in the bodily tissues that render them no longer suitable for growth of bovine and possibly more suitable for the growth of human tubercle bacilli." A satisfactory discussion of the shifting of the ratios of the two types of infection in later childhood would involve too long a digression to be made here; but it may be pointed out that there has thus far been no evidence whatever that puberty alters the characteristic *tissue* response to tubercle bacilli. On the other hand, it has been abundantly demonstrated that infection does: at any age it promptly enhances greatly the ability of all tissues to meet the germs exudatively rather than proliferatively. In other words, it ushers in hypersensitiveness or allergy. At the same time, if increased mortality is to be our measure, we are prone to associate puberty with falling resistance.

Among the ceaseless and uniform changes that are going on in the body from birth to old age, it so happens that they plainly affect one part of the body which, by common consent, has much to do in resisting the march of tuberculosis. This part is the lymphatic system. Among its several functions is the major one of limiting the spread of infections, and in no infection is this office so manifest and so well performed as in tuberculosis. Whether tubercle bacilli are inhaled or ingested, practically every natural infection begins at that moment when they shall have passed the mucosal epithelium and have gained the submucosa. Here, between the cells of a bodily structure, they are always, first, within the province of the lymphatic system; and all that are conveyed further will, within a microscopic distance, be carried into lymphatic vessels and proceed by these for variable distances. At countless places they will meet with intercalated collections of lymphoid cells that range from the minutest aggregations to large lymph nodes.

Every collection of this kind is a more or less competent bar to the further central progression of the bacilli; more or less competent as the texture of the lymphoid mass is more or less dense and compact, as

(think some) the channels within the mass are narrower or wider, or more or less tortuous, or the flow of the lymph is sluggish or rapid, of low pressure or of high.

The net result of this enormously developed and complicated mechanism is that, if we consider tuberculous infections as a whole, the lymphatic system in man becomes the great repository of infection. Lymph nodes are, above all other loci, those where function goes on undisturbed and unimpaired. Persistent—permanent—infection of lymph nodes has its dangers, many of them, that need not be elaborated. But, in general, lymph-node infection is the most favorable that occurs. In the vast proportion of cases it remains completely quiescent. When it is active, it disturbs the body less, and less frequently, than would *similar* processes in any other location. But, above all, it reduces the ravages of tuberculosis by delaying or preventing its spread.

We think of greater or less resistance to tuberculosis in terms of the latter's capacity to spread throughout the body. A limited process arouses the idea of good basic resistance; a spreading one of failing resistance, of resistance declining in proportion as extension is farflung or rapid. It is impossible to escape the idea that one of the resisting functions of allergy lies in the latter's ability to fix bacilli promptly where they settle and thus impede or prevent their further distribution. Lymphoid masses will act similarly, though in another way. In every instance in which infection is established we must believe that both the lymphatic system and allergy are contributing their part to the sum total of resistance.

Our knowledge of the anatomy and physiology of the lymphatic system for the several ages of man is not as complete as we might wish, but about it there are several features pertinent to our inquiry that are well established. In general, it progressively undergoes an anatomic change from birth to maturity. Throughout infancy and early childhood there takes place an increase of adenoid tissue. The structure of the lymph nodes is then characteristically open and loose; the amount of cellular material is relatively low, fibrous tissue is slight, spaces are wide, and often the cross section of a smaller and more immature node will appear as a mere shell of lymphoid tissue enclosing a network of large, open sinuses. Foreign deposits in exposed nodes (for instance, the tracheobronchials) are slight. Lymphatic vessels are abundant, open, and in exposed organs (such as the lungs) comparatively free from foreign deposits in their walls. The entire architecture gives one the

impression of an "open" lymphatic system, in which movement is free and active, and spread from point to point, and on through nodes, relatively facile. If, now, one remembers that the activity of lymphatic flow reflects that of the blood and, in addition, that the infantile and puerile circulation is peculiarly active and sensitive, one's opinion of an energetic lymphatic function during the early years is strengthened.

From early childhood on, the lymph nodes are continually growing more solid through an increase of their cellular components. From birth to adolescence the entire tendency is for the nodes to become denser and more compact structures,—to form masses that are progressively increasing in capacity to intercept and hold particles (bacteria) that may come along with the lymph-stream. At the same time, foreign material accumulates along the lymphatics and in the lymph nodes, particularly in certain parts of the body such as the lung. This deposition, together with the frequent irritation caused by intercurrent diseases that affect the lymphatic system, also brings about an increasing fibrosis.

As maturity is established the lymphoid tissue of the body tends to atrophy, an inclination that is more marked as age comes on. The nodes shrink, and become still more compact and "tighter," as we observe so commonly in the case of the tonsils; and in organs open to the reception of foreign particles, such as the lungs, the lymphatics are more and more surcharged with them.

It is plain that in the normal evolution of the lymphatic system during life, we have a "drainage" apparatus that from infancy and early childhood on is becoming more and more blocked. From birth to maturity facility of transport grows less and less. Early in life particles may be conveyed along distances before coming to rest, but as we advance in years, with the same propelling force behind them, they would have a tendency to make shorter and shorter journeys; until a condition is arrived at when the average movement along lymphatics is minimal.

Under these circumstances an infection such as tuberculosis has an inclination to spread in early life and remain more localized with increasing age; that is, *so far as the lymphatic system is concerned.* If, then, we conceive of resistance as being, to a great extent, a composite of two bodily forces, namely, of a succession of more or less sufficient lymphatic barriers, present in varying integrity in all human beings, and of an allergy and immunity acquired by infection, we arrive at the opinion that *lymphatically* the generality of children are less resistant than are adults, while *allergically,* for the reasons stated above, the *generality*

of *infected* adults are less resistant than are *infected* children. In other words, noninfected adults should be more resistant than noninfected children, for they are so constituted that first infections cannot spread with the same facility as in children. But the allergy or immunity gained by infection is likely to be greater in more infected children because of the shorter interval that has elapsed than can have been the case in the general run of adults with old-standing infection.

In the noninfected child, then, a sufficiently large infection has a bent toward early distribution, and any metastasizing infection may spread more easily, by way of lymphatics, than in adults. On the other hand, the relatively high allergy of the infected child operates markedly to mitigate the danger of this basic facility of metastasis, for one of its effects is to fix, and thus limit and retard, the extension of bacilli that may be conveyed lymphatically or otherwise.

Both of the above suppositions are borne out by experience. As a class, infected children give more vigorous skin reactions to tuberculin than do infected adults and are therefore more allergic. At the same time, a tendency to spread is perhaps the most striking characteristic feature of childhood infection and is in marked contrast to the more common localizing habit of adult tuberculosis. If, now, we bring into association the two childhood properties of (1) relatively immature lymphatic check to the movement of tubercle bacilli and (2) comparatively high allergy, we begin to find ourselves in a position to explain some prominent features of childhood infection that have been rather puzzling. Why, for instance, are so many children hardly or not at all ill though tuberculous infection is widely distributed in the body? Why will the child's lungs accommodate much infection, yet the child will exhibit slight or no symptoms of pulmonary tuberculosis?

A child breathes in tubercle bacilli, and these pass through the bronchial or alveolar epithelium and are then conveyed to the hilum; and at the hilum the evidences of infection become most prominent. Or the child develops manifest infection of its cervical lymph nodes, when, if we examine and observe the patient carefully and frequently enough, we may find a widening mediastinal shadow; that is to say, infection is spreading from neck nodes to lung root by a pathway that must be lymph vessels to veins, to lung, to lung lymphatics, to lung lymph nodes. The same accretion of lung-hilum infection may be noted in children with peripheral processes anywhere (see fig. 1).

Or the child ingests bacilli repeatedly, no doubt in large numbers with its milk, and infection is wont to pass the intestinal mucosa and appear prominently in mesenteric lymph nodes, and in retroperitoneal and lung-hilum nodes as well. *Intestinal* foci are not nearly so common in children as in adults, though we are accustomed to assign to the former ample opportunities for infection by ingestion.

Under similar conditions adults have processes locate *in* the lungs and *in* the intestines. Their lymphatics do not convey bacilli so completely away from the portal of entry in the organ concerned. At the same time, the allergic condition, more common to adult life than at the earlier ages, adds to the "fixing" or arresting action of a less open and active lymphatic system. In adults, of whom the larger part are infected and allergic, there is *characteristically* a summation of forces to retard the spread of bacilli. In children the situation is either one of facile lymphatic conveyance in the uninfected, or the interplay of two opposing forces in the infected. We must believe (as has been stated previously) that, in general and unless an adult's allergy is occasionally revivified by reinfection (metastasis), the allergy of the infected child is greater than that of the infected adult. Such a child possesses, therefore, a high capacity to arrest *in situ* the germs of reinfection (metastasis). But this attribute is largely balanced, and very frequently outweighed, by the imperfect lymphatic checks to the progression of bacteria. In infancy both lymphatic vessels and lymph nodes are more open than at any other period during life: accordingly, much localization of infection in lymph nodes is the uncommon event, as meanwhile the infection spreads widely. With childhood the lymph nodes become denser, although lymphatics still remain unobstructed; and we now enter a period of the highest incidence of marked lymph-node infection, although the tendency to spread continues great: in the nodes there is likely to take place an accretion of germs conveyed by active lymphatics. With increasing age the lymphatics of those parts most exposed to tuberculous infection become less and less active in moving bacteria from portals of entry, as, too, collections of lymphoid tissue (for instance, the tonsils, intestinal follicles) grow less permeable to bacteria which enter them.

In the circumstances, therefore, if there are given the same type of peripheral foci or the same opportunities to receive infection into the same lymphatic nexus, bacilli are much more likely to pass along the lymphatics and on to lymph nodes, and to continue to accumulate in the latter in children. As a consequence there is much more evident lymph-

node infection in children. And it happens that although their lymphatic systems permit easy transport, and thus lay down more opportunities for progressive infection, the vastly greater tendency for infection to be concentrated in the nodes is favorable rather than otherwise. For, as has been stated above, lymph-node infection is of a relatively benign type, largely for reasons of location. In general, it spares the body from organic tuberculosis and, thus, more marked functional derangement; and well-functioning lymph vessels, by conveying bacilli *through* and *from* organs on to the latters' lymph nodes, contribute tellingly to this result.

I have, in another place,[7] recently discussed at some length the common occurrence in children of widely distributed, though generally benign, tuberculous infection. Not enough attention has thus far been paid to this type, though an enlarging knowledge of tuberculosis, which an increasing use of infection tests and of roentgenography and a wide appreciation of the milder manifestations of infection will bring about, will no doubt impress us in time with its frequency and call for explanation. I cannot go into the matter with much detail here. But the facts are that a very large number of children, who are slightly and often indefinitely ill, can be shown to possess foci of tubercle in several widely scattered locations, that this number increases as we apply our methods of detection more regularly and extensively, and that, in general, the outlook for these patients is anything but gloomy. In short, in ailing children with tuberculous infection, it is the more usual thing to find tubercle at more than one place, and it is more common than otherwise for these patients with several demonstrable foci to be only mildly ill.

The ailment may be a minor eye affection, perhaps phlyctenular conjunctivitis. The patient is otherwise without complaint. The Pirquet test is positive. There are hypertrophied tonsils and enlarged cervical lymph nodes. The enucleated tonsils may exhibit tubercle on microscopic section. Clinically, the neck condition is tuberculosis, though relatively inactive. Routine X-ray examination of the chest discloses a markedly enlarged mediastinal shadow with patches of increased density extending out into the lung.

Such a combination (or variants of it) is by no means a rarity in our dispensary practice. Its frequency is quite impressive. The above

[7] *The Spread of Tuberculous Infection in the Body*, AMERICAN REVIEW OF TUBERCULOSIS, 1924, ix, 83. Cf. also *Experimental Studies on Tuberculous Infection*, Ibid., 1922, vi, 1.

case would mean infection in five separate places that can be proved. One child may complain of its eyes, another of the lumps in its neck, a third be without external local disturbances but evidently run down and perhaps pale and listless. Some may have transient eruptions of tuberculids; others involvement of a bone or joint; few of this type will be ill with pulmonary symptoms. But, whether the patient enters the dispensary by way of the orthopoedic or laryngological or dermatological or ophthalmological clinic, roentgenographic involvement at the hilum of the lung can be made out with few exceptions; and sometimes infection may involve as many as six or seven widely scattered locations yet the patient never become strikingly ill.

These children must surely have processes that because of their recent evolution have not had enough time to be well invested, processes that readily send over infectious grafts to the proper channels of distribution. They surely must also have open and active avenues of transport. Unopposed, both of these peculiarities would doom such children to ready destruction by tuberculosis. But, to counteract such potential mischief, the children have, in addition, an allergy and immunity that are high, and they also have lymphatic systems that sweep a large proportion of infectious material along to lymph nodes which, though capable of caring for much of it, fall manifestly diseased themselves if the amount that they can endure is exceeded or if their functional integrity is upset by other events (for instance, acute or chronic inflammations of the mouth and throat). And since the lymph nodes of the lung hilum are the receiving station of all particles that pass into and through the lymphatics of the lungs, and the lungs are the destination of all nonintercepted particles that come by lymph and blood from the periphery of the body, the hilum nodes bear the brunt of tuberculous infection no matter where this is localized in children.

The case which follows will illustrate several of the points touched upon above. Some of its features are extreme examples of their kind, but *fundamentally* the case is an average specimen of tuberculous infection of a large proportion of our child patients. It illustrates the transport of infection to the hilum, though the first focus was extrapulmonary; the piling up of infection here as peripheral foci progress; the absence of pulmonary symptoms as long as pulmonary infection is confined to the hilum, even though the evidences of infection here may be extreme; and the relatively mild illness that children will for a long time exhibit while suffering from extensive and scattered infection.

Harry R., colored, aged 6, was brought by his grandmother to the tuberculosis Dispensary on March 6, 1923. The grandmother had raised the boy, whose parents were separated, the mother living in Detroit and sending home small sums of money irregularly, while the father lived in Baltimore but contributed nothing to the child's support. The grandmother's household lived in a three-story, nine-room brick house, very dirty and in bad repair, and unheated in winter except in the kitchen and dining room. Together with a brother, aged 9, and a cousin, aged 4, the boy slept in a room with his grandparents. *Both brother and cousin were found later to be negative to tuberculin*, as was another cousin who lived in the same house. None of the children got milk in their diet because the household could not afford it. The grandmother was of the "oldfashioned" type of colored woman, illiterate, hard working, conscientious, devoted to the sick boy, and giving him all the attention possible during the time that she was not employed outside the home.

The boy's past history was indefinite except that one year previously a lymph node had been removed from his neck by surgical operation. He had not suffered any known exposure to tuberculosis. He had not been ill before, save for the operation on his neck, though his grandmother had considered him always a "delicate" child.

He was brought to the dispensary because of lumps that had recently appeared in his neck and extremities. About three weeks before, he had complained of a swelling in the neck. A few days later he fell and hurt his right ankle and he had been limping since. Five days before admission he showed his grandmother his right hand and elbow, both of which were swollen.

He was undersized and somewhat undernourished, but without fever and not acutely ill. In his neck was a large swelling that was evidently tuberculous. At the right elbow was a fusiform swelling of the ulna, deforming the joint, and firm and tender with slight increase of local temperature. The right carpus and metacarpus (radial aspect) were similarly involved; and here there were fluctuation and rather marked participation of the soft parts in the process, and fulness of the palm. The right ankle was quite swollen behind, from the malleoli to the plantar surface of the foot. Here, too, there were evidences of slight inflammation and the fulness seemed to involve mainly the soft parts.

Percussion of the chest elicited no abnormalities over the lung areas, but resonance was diminished over the manubrium and upper spine. Breath sounds were harsher on the right side than on the left, particularly in the right interscapular region. There were no râles.

The clinical first impression was tuberculous cervical adenitis, tuberculosis of the right ulna, metacarpus and carpus, tibia and os calcis, and tuberculosis of tracheobronchial lymph nodes.

The X-ray of the chest disclosed the extraordinary mediastinal shadow shown in figure 1. The X-ray report of this read "either enlarged heart shadow like pericarditis or unusually large mediastinal glands," and "remains of thickened pleura at the right base." That of the bones was "Osteomyelitis of upper end of ulna and of os calcis; periostitis of carpal bones. While the chest may be tuberculous, the bones suggest a pyogenic infection."

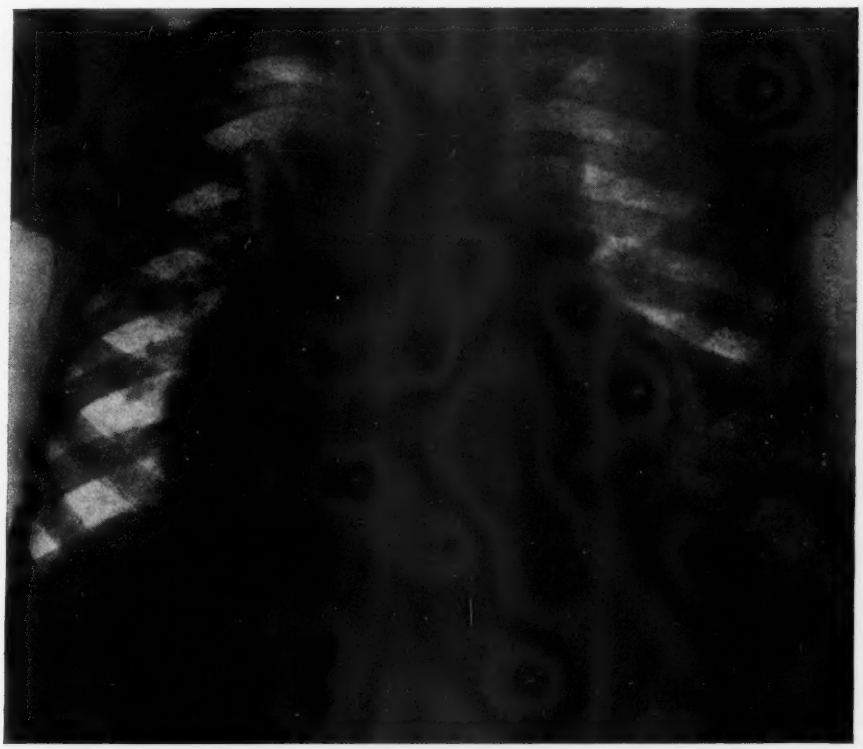

FIG. 1. PATIENT HARRY R., NEGRO CHILD, SIX YEARS OLD

Onset of clinical tuberculosis with cervical adenitis, one year before skiagram of chest was taken in 1923: enucleation of cervical lymph node in 1922. Recurrence of cervical adenitis and development of multiple foci of bone tuberculosis and scrofuloderma. Infection due to human tubercle bacillus. No development of symptoms of pulmonary tuberculosis. Enormous mediastinal shadow persisting until death from bronchopneumonia in June, 1924.

Diagnosis of the bone condition became positive when, almost six weeks later (April 13), the abscess in the hand was aspirated and acid-fast bacilli were found in the withdrawn pus. Cultures were made of the pus, from which pure cultures of tubercle bacilli developed. The latter were further determined

as of human type because of normal pathogenicity for guinea pigs and low virulence for rabbits (1 cgm.)

A second X-ray of the chest (March 27) brought the report of "huge mediastinal mass with some extension down at right base, suggesting a growth rather than a tuberculous lesion." A third X-ray (April 24) was read as "marked enlargement of mediastinal glands, tuberculous in origin."

It became plain that here we were dealing with a case of multiple peripheral foci of tuberculosis with exceptional central (tracheobronchial) involvement. The patient's past history yielded a single relevant episode, that of a cervical lymph node removed one year before the almost simultaneous appearance of several tuberculous processes, the first of which was again a swollen node of the neck. The neck involvement of a year before was surely tuberculous. Its situation makes almost necessary the opinion that it represented the site of primary infection in the body. To account for the tracheobronchial lymph-node process we must assume (1) that infection proceeded there from the cervical-node tubercle, or (2) that it came from inhaled bacilli, or (3) that it was the result of bacilli carried back by lymphatics (and then blood and then pulmonary lymphatics) from the several active bone and scrofuloderma foci that had latterly developed.

It is because there was known tubercle at a site like the cervical lymph nodes a year previously that one inclines to the view that infection of the tracheobronchial nodes came originally from the neck nodes, and was set up by those bacilli which, in their transit, were carried out of pulmonary blood vessels and into pulmonary lymphatics. Perhaps the several bone foci were laid down months before they became manifest, and had originated from bacilli that passed through the blood vessels of the lungs and on to the systemic arterial system, or through bacilli that were mobilized at surgical operation. But, once in active evolution, the bone infections might readily send bacilli over to the lymphatics and thence to the venous blood; when, since the patient was a child, few germs "stuck" in the lungs but continued by open lymphatics to the hilum nodes, to add to the infection there.

During all the time that the enormous involvement of the tracheobronchial nodes was developing, the patient had never a single symptom referable to his lungs. As has been noted, he did not appear very ill on his first visit to the dispensary. He returned often for tuberculin treatment and for the whole of the first month was always without fever. Then, in the first part of April, he developed a sore throat and he began to have fever. On April 24th, forty-nine days after his first visit to the dispensary, it was noted for the first time that he had two swellings on the anterior chest wall, both on the right side. One was over the fourth rib, close to the sternal border; the other was over the third rib and just above the right nipple.

During April the boy failed visibly, and on May 1st he was transferred from

the ambulant patient service of the tuberculosis dispensary to the Harriet Lane Home, where he became a bed patient. When he entered the latter he had cold abscesses of the right elbow, wrist and ankle and of the chest wall. None had ruptured, but all were then fluctuant. Underneath all were involved bones. Except for abnormally wide substernal dulness the lungs were practically negative on physical examination. There were no pulmonary symptoms. The boy was plainly weak and malnourished, he had little or no appetite for food, and he had fever of a daily range of from about 99° to 101°.

He remained in the hospital throughout the summer, for four and a half months, from May 1 to September 16. Constitutionally he did fairly well. He soon regained his appetite and felt much better; the phrase "feels fine" recurs frequently in the progress notes during the summer. There were irregular periods of fever that during May would reach 102° or 103° daily, that became lower by June, and that through August tended to fluctuate between 99° and 100°. During September the average maximum temperature was about 100° up to the day of discharge.

About the middle of May the abscesses of the hand and ankle ruptured spontaneously; one month later that of the elbow broke through, and at this time the abscesses of the chest wall were becoming confluent. On August 13 the latter also ruptured. All abscesses continued to discharge throughout the remainder of the boy's stay in the hospital.

For several weeks in May râles were heard in his chest; but these soon disappeared. He never had lung symptoms. His discharge reads, "On discharge there were no signs in his chest other than those caused by the abscess discharging on the anterior chest wall and by the enlarged mediastinal glands (pushing (?)) the apex beat out 1 to 2 cm. beyond *m. c. l.*" His weight on discharge was 40 pounds, or 1 pound, 6 ounces greater than on admission to the ward. His daily range of temperature was then 2.5° to 3° as against 4° to 4.5° shortly after admission.

From the hospital the boy was taken to his home and, after a little more than a month there, was removed to the Municipal Hospital (almshouse) at Bayview. Here he gradually failed, and died June 24, 1924. Several X-rays of his chest were taken during his stay at Bayview, including one three weeks before his death. Reports of them always stated that, although the enormous mediastinal shadow persisted, the lungs were "clear." Meanwhile the boy never had any lung symptoms, nor did any new areas of superficial involvement develop. The tuberculous abscesses kept open and draining, as the symptoms of intoxication—anaemia, loss of appetite and weight, fever—progressed. The cause of death was given as bronchopneumonia.

There may always be legitimate grounds for dispute as to the significance, particularly as regards etiology, of enlarged and widened

mediastinal shadows in children who are free from symptoms of pulmonary disease. There can be no disagreement about the cause of the root condition in this case, with its abundance of suppurating tuberculosis at other parts of the body. An extreme example, it demonstrates unerringly where infection can go when peripheral foci exist to "feed" bacilli to more central locations. Our experience leads us to look upon this transference of infection to the pulmonary hilum as the common occurrence in children. Time and again, if we make roentgenological examinations of the lungs of the same patients at intervals, we are impressed by a changing hilum shadow that "keeps pace" with the progress of other foci at distant points, such as those of cervical lymph nodes. We would not imply that the association is an invariable occurrence, but it happens frequently that while tuberculous cervical lymphadenitis is at its height there is a noticeable and (in the circumstances) abnormal widening of the mediastinal shadow, which again narrows as the process in the neck subsides. We have observed the mediastinum to behave similarly with the coming and going of phlyctenular conjunctivitis, which is so frequently on a tuberculous basis; while, of course, root changes in connection with manifest tuberculosis of the bones and joints are a commonplace.

We agree that there is slight justification in insisting on the tuberculous nature of minor degrees of mediastinal enlargement in children who present no other evidences, anatomic or symptomatic, of tuberculous infection: several conditions other than tuberculosis may bring about more or less protracted changes at the hilum. But it is no less true that in children, who are not affected with nontuberculous pulmonary disease or chronic diseases of the upper respiratory tract and its appendages, and who at the same time possess other indubitable earmarks of tuberculous infection, there is no good reason to consider hilum changes anything else than tuberculous and there is every likelihood that they are tuberculous.

The case presented above also illustrates tellingly how excessive tuberculous hilum involvement may be without its giving rise to local (pulmonary) symptoms. Clinical experience has always taught us that tuberculous infection of the hilum with local symptoms is the rare event, almost the exception, when the root is involved. Constitutional symptoms of the condition are much more frequent, yet it is the rule for these to be vague and indefinite and contributing to a general state of indifferent health which we are accustomed to designate as "run-down" or

"under par." But, if the data were obtainable, we would predict that the vast majority of children with infected hilum would show no symptoms whatever and no signs except a (frequently equivocal) widening of the mediastinal shadow.

In practice the diagnosis of tuberculous hilum infection in children only mildly ill is no doubt overlooked far more frequently than it is made. In such children it becomes largely a diagnosis by elimination and the application of several procedures that elicit collateral evidence (skin test, etc.). Yet it is likely that if the standards laid down by Hawes (8) were rigorously followed, the condition would become a definitely and correctly diagnosed disease. We believe that in the absence of detectable nontuberculous conditions a widened mediastinum in a child who reacts positively to tuberculin warrants a presumptive diagnosis of tuberculous infection of the hilum, whether the child is or is not ailing.

All in all, it is difficult to comprehend the logic of the frequently expressed warning that makes a sharp distinction between children and adults in respect to the dangers of exposure to tuberculous infection. It certainly is by no means clear that, person for person, the child is less resistant than the adult. As it works out in life, it is beyond dispute that the ravages of tuberculosis are in every way greater in later life than in childhood; and, even allowing for differences of environmental factors that determine illness, we would consider the proposition of a higher adult resistance as unproved. There are elements of resistance that would seem to be stronger in the child; there are other elements that appear more effective in the adult. Where the balance lies we do not know; nor may we assume to state. Quite likely it is an individual affair, and attempts to generalize promise to lead us into error.

It would seem the better wisdom to presume not at all upon a resistance, an acquired immunity, that must be of undeterminable and hypothetical integrity in any particular case. We shall be following the larger science and come to a safer practical result if we adjudge children and adults alike before the hazards of tuberculous infection. *The only rational attitude is to protect all human beings, of whatever age, against exposure.* To allow the impression to get abroad that adults walk within a charmed circle of acquired immunity, that maturity is a privileged age, can lead only to evil, if it is accepted and acted upon. Besides, there is much evidence that it may be far from the truth.

It has been the fashion to put infants in a special class as regards their resistance to tuberculosis. Infancy, so it has been taught, is the period of extreme and greatest susceptibility. Infection then results almost inevitably in illness and illness in death, and, since the usual mode of fatal termination is generalized miliary tuberculosis and meningitis, by a reciprocal relation of concepts the occurrence of the latter has come to stand for the marks of a low resistance.

There is no doubt that our idea of the peculiar lack of resistance of infants arose out of and was long entertained through imperfect knowledge of tuberculous infection of infants. Until a little more than a decade ago our acquaintance with it was limited almost entirely to its progressive and fatal forms. We had no way of detecting its presence in the absence of plain symptoms and signs, and the recognition of its minor manifestations was quite faulty and incomplete. Naturally, therefore, when meningitis and generalized miliary tuberculosis were about the only evidences of the infection that were thought to occur in infancy, the idea of its inevitable gravity and fatality for infants entered into our tuberculosis concepts.

But infection tests, roentgenography and a better appreciation of the etiological nature of some symptoms and signs, such as skin eruptions and obscure elevations of temperature, have thrown a much fuller light on infantile infection.

We may be certain, for instance, that the number of infected infants is several times that of those ill with tuberculosis. Infection tests, performed thus far, indicate that, on the average, about 10 per cent of the general run of dispensary infants of one year of age react positively. Of course, the number dead or ill from tuberculosis at this age is nowhere near this proportion;[8] and these newer facts of the evidence of infection must surely make us revise our older ideas of the extreme gravity of tuberculous infection, *as such,* for young infants.

The more I see of tuberculosis in infants and the more I confirm diagnosis by the aid of new methods, the more tuberculous infants I find who run along with comparatively little illness and withstand their infection well. My experience of the last few years has convinced me that (1) many infants become infected and never fall ill with tuber-

[8] During 1915 to 1920 the tuberculosis death-rate for male infants, from birth to four years, in New York City was 150 per 100,000 alive. The infection incidence was surely as high as 10 per cent, or 10,000 per 100,000. On this basis, it would appear that only one of every 66 *infected* male infants died from tuberculosis.

culosis, (2) in many there are symptoms, but so slight and indefinite, as to have their real significance unappreciated in ordinary practice, and (3) many even of those who exhibit symptoms of illness due to tuberculosis make good recoveries. In this connection I append two striking instances, not unusual as cases of infantile tuberculosis of benign type, but illustrating the importance of making use of all our diagnostic agencies if we are to have a proper apprehension of tuberculosis in early life. It is also true that we will gain in fulness of judgment only as we follow the subsequent career of these little patients and make repeated observations on them over a period of years.

F. B. S., male, was born April 24, 1922, the second child of young and healthy American parents, in comfortable circumstances and living in the country. He had a sister born just two years before, who had never been ill. He was breast-fed until January, 1923, when he was put on cow's milk. He was reared exceptionally sheltered and well cared for, sleeping in a room with open windows from birth, spending much of the day on a sunny porch and never taken from home except for the daily airing in his coach and go-cart. The mother, without a nursemaid, had entire charge of the infant from birth. Besides the immediate family, the baby had no other associates except his paternal grandmother who at intervals lived with the family for several months. There was no suspicion of tuberculosis in any member of the family.

The infant developed normally and was always unusually healthy. Its first upset was in February, 1923, when ten months old. Then, at the end of a normal day, it refused the bottle and became restless and peevish in the evening. It was found to have a temperature of 104°. The next morning it was apparently as well and happy as ever, and continued so for a month. In March it again suddenly became upset as before and was found to have fever, which this time also lasted only for one night; and the next day the baby was in apparently its usual health.

On April 17, 1923, I was asked late in the afternoon to come to the house to see the baby, who had just been brought in from its daily airing. The mother had then noticed an eruption on the infant's face. He seemed perfectly well and happy and playful. On the forehead and both cheekbones was an eruption, rectangular on the former and circular on the latter. It was a vivid scarlet and sharply circumscribed and, since the baby did not try to scratch it, apparently nonitching. During the next two days the eruption gradually faded.

Meanwhile the baby did not appear ill. On the evening of April 19 it refused food and was restless, and had a temperature of 102°. The next day it was again in its usual good health but toward evening developed fever and

restlessness. It went through the next two days in the same way, that is, apparently thoroughly well, hungry and lively during the day, and febrile and unsettled as night came on. During the night of April 22 it became quite

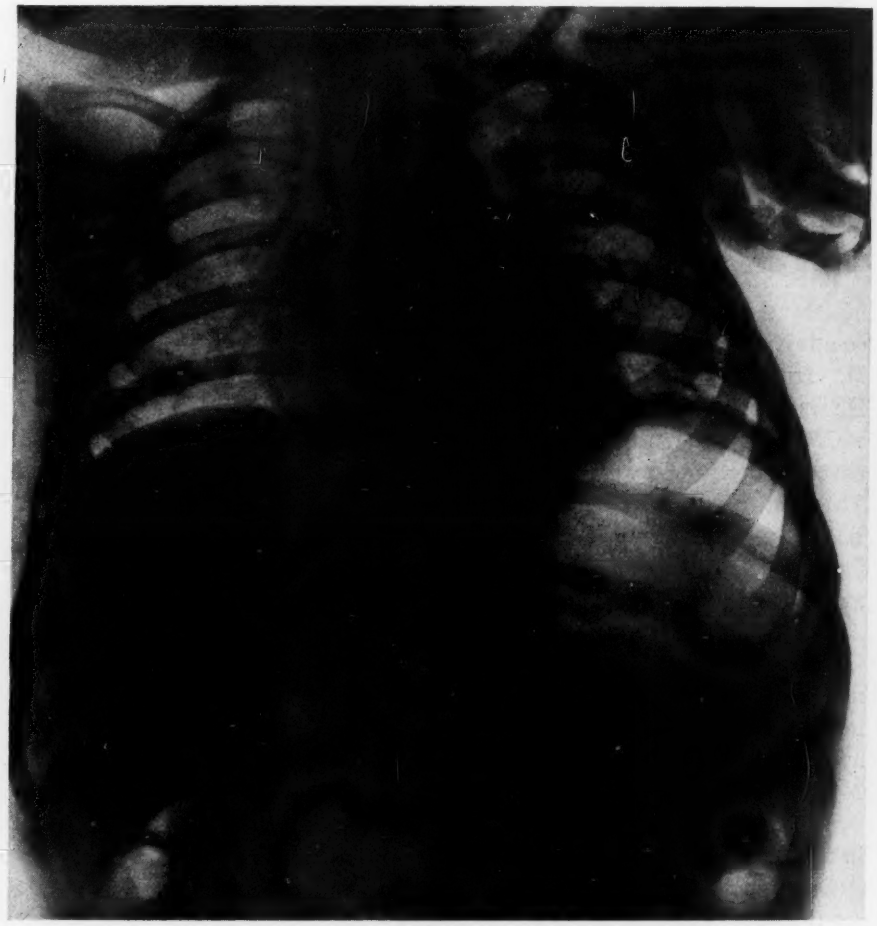

FIG. 2. PATIENT F. B. S., WHITE MALE INFANT OF AMERICAN PARENTAGE, ONE YEAR OLD

Born April, 1922. Breast-fed. Weaned in January, 1923, and put on unpasteurized cow's milk. One night of fever in February, 1923, and again in March. Remittent fever for six days in April, 1923, and tuberculids at end of febrile period. Vigorous skin reaction. Enlargement of hilum shadow with evidence of infiltration on the right. See also fig. 3.

ill and grew steadily worse during the night, until at six o'clock on the morning of the 23rd its temperature was 106° and it had a convulsion. By noon of the 23rd the temperature had again fallen to normal, when the baby again promptly recovered its appetite and appearance of general well-being. The

night of the 23rd it was without fever and slept normally, and awoke on the morning of the 24th lively and well. But toward noon it again began to appear ill and at 1 P.M. was found to have a temperature of 103°. It was then brought to the Harriet Lane Home of the Johns Hopkins Hospital and admitted here as a patient.

On admission to the hospital, at four o'clock in the afternoon of April 24, the infant's temperature was 103.2°. Thorough physical examination disclosed nothing abnormal, except the fever, and there were no localizing symp-

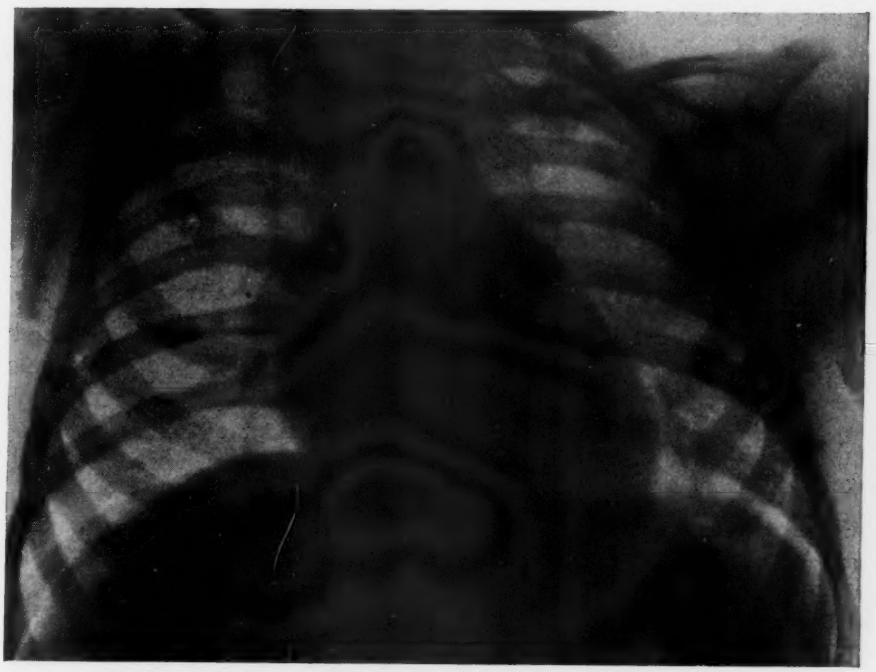

FIG. 3. PATIENT F. B. S., TEN MONTHS AFTER SKIAGRAM OF FIG. 2

Patient now almost two years old. Has been in perfect health since fig. 2 was taken. Hilum now clear. Skin reactivity much diminished. See also fig. 2.

toms or signs. The history of the illness, particularly the septic type of the fever, suggested a condition like pyelitis, but examination ruled out this condition. A few hours after admission the baby was given a Pirquet test.

The temperature fell rapidly and was normal at 8 A.M. on April 25th. The baby now appeared completely well again. The skin test (intracutaneous) *was vigorously positive.* An X-ray plate of the thorax showed "enlarged mediastinal lymph nodes and beginning root infiltration, suggesting tuberculosis." (See figure 2.)

The baby remained in the hospital for six days, but had no more fever after the early morning of April 25th, and seemed perfectly well. But on the 26th, while afebrile and in apparent health, a "measly" eruption developed on the trunk and neck. This was "reddish, raised and maculopapular." There were at the same time no Koplik's spots, conjunctivitis or fever. During the next two days this rash slowly faded and by April 28 was practically gone. On the 30th the baby was discharged from the hospital. He was then just a year old, was $30\frac{1}{4}$ inches tall and weighed $19\frac{1}{2}$ pounds.

The eruption was diagnosed as being *tuberculids*, and no doubt correctly so. The circumstances of its appearance resembled somewhat the behavior of a case of frequently recurring tuberculids which I saw several years ago. This latter case was that of an infant who for months, at intervals of several weeks, had successive crops of tuberculids of almost inconceivable variety. Ordinarily, the infant's temperature would continue about normal, to be punctuated at intervals with sudden bursts of high fever, which would last for a day or two and be immediately followed by a new eruption. This baby died after a long stay in the hospital.

After leaving the hospital the patient remained well and has continued so until the present time, when it is three years old. During the remainder of 1923 it never experienced the slightest illness, except for one night of fever and fretfulness without assignable cause in July. On February 29, 1924, ten months after discharge from the hospital and when 22 months old, the baby was again thoroughly examined. Physical examination was completely negative. X-ray showed that the signs of hilum involvement had now disappeared (fig. 3). Intracutaneous test was still positive, but the reaction was much weaker and more transient than in 1923: at twenty-four hours there was an areola of redness, 15 x 20 mm., with slight induration; at forty-eight hours the reaction had faded altogether. The baby's weight was now 28 pounds.

This case, one of undoubted tuberculous infection and illness in the first year of life, would almost certainly have gone undiagnosed or have been wrongly diagnosed in active practice. We cannot believe that it is unique. Reuben and Smith (9) have lately reported a survival incidence of 32 per cent of 64 children who were proved to have been infected during the first year of life: one of these, who developed cervical adenitis and had a positive Pirquet reaction at three months, remains well at two years of age. No doubt most or all of Reuben and Smith's subjects had progressed to the stage of illness with tuberculosis. It is certainly true that many infants suffer infection without becoming ill,—in substantiation of this statement we need only point to the incidence of infection under two years, as determined by Pirquet tests. If, there-

fore, we had only reasonably complete data of tuberculosis in infancy—data that are almost wholly lacking at present—we would almost surely find that a large proportion of infants withstand tuberculous *infection* not only successfully but also without ever being made ill by it. Reuben and Smith also mention how insignificant the clinical evidences of infantile tuberculosis may be: "the reaction to the initial infection in these cases is so slight that it is often missed." And they are quite correct in pointing out that the condition is frequently "diagnosed as due to teething or influenza," and (one may add) to a number of other affections.

The above case also illustrates the demonstrable strides toward healing made in less than a year in an infant. Within ten months all pulmonary abnormalities disappeared from X-ray observation, and a vigorous skin reactivity became comparatively weak. It is unfortunate that the child has passed from under my direct observation, for if I could now, after two years, make a third annual examination, I might reasonably expect to find even skin reactivity in abeyance. I have always considered the case to be one of probable (though unproved) bovine-bacillus origin,—the first symptoms came on about five weeks after the baby was put on unpasteurized cow's milk. But the following remarkable case in one due undoubtedly to the human bacillus.

In 1917 a pregnant woman was referred by the Obstetrical Clinic of the Johns Hopkins Hospital to the Tuberculosis Dispensary. She was found to have quiescent, fibroid pulmonary tuberculosis and, as a routine measure, the social service worker of the dispensary was sent to the woman's home. Here the former found an Italian family of father, mother and three children, aged one, five and eleven years, living in two rooms. The father was ill with pulmonary tuberculosis and unable to work. His left lung was extensively involved (with cavitation) and his sputum positive for tubercle bacilli. He also had ulcerative laryngeal tuberculosis. The three children were brought to the Tuberculosis Dispensary and, although they appeared to be in the best of health, all were infected.

The youngest was a girl, Josephine L., born February 11, 1916. She was first seen at the dispensary, when sixteen months old, on June 23, 1917. *Since birth she had slept in the same bed with her father and mother.* The best history that could be obtained from these people, who spoke no English, was that the father's illness began with cough in April, 1917, although he had been unable to work since March. At this time the little girl would have been thirteen or fourteen months old; and the presumption is that her exceptionally close con-

tact with infection antedated this age. On her first visit to the dispensary she was given a Pirquet test which resulted in an extreme reaction that involved almost the entire flexor surface of the forearm and finished with a slough and scarring. This scar was photographed in 1923, six years afterward, and is shown in figure 4, as an instance of the remains of what a Pirquet reaction can be. The little girl's two brothers reacted almost as vigorously.

Here then we have a case of tuberculous infection, that is undeniably of the human type, taking place first at surely one year of age and quite likely before this. Between 1917 and 1923 I saw the little girl occasionally at long intervals,

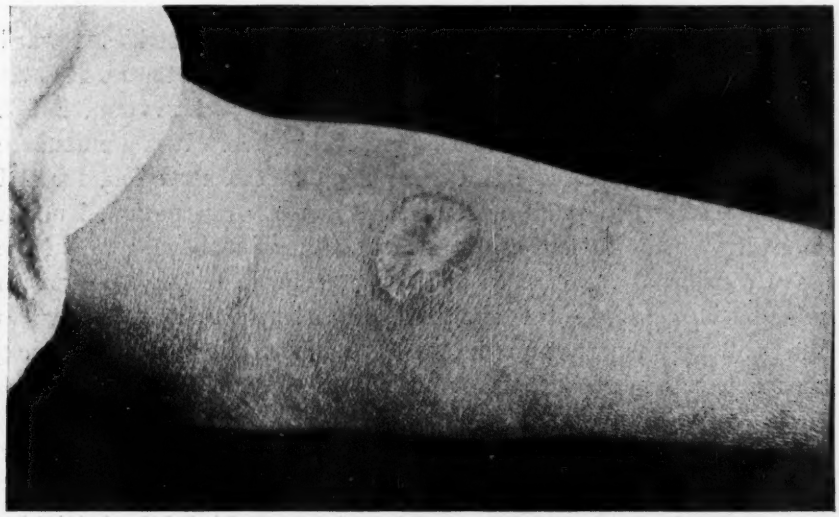

FIG. 4. PATIENT JOSEPHINE L., ITALIAN CHILD, PHOTOGRAPH OF ARM, 1923, SIX YEARS AFTER SKIN TEST REPRESENTED BY SCAR

Patient born in 1916. Slept in same bed with phthisical father from birth. First observed in 1917, when one year old, when patient reacted violently to Pirquet test. Scar of this reaction shown herewith. See also figs. 5 and 6.

and since 1923 annually. She was in outward health when I first saw her and, except for eye trouble, she has since had an unusually healthy childhood. Her photograph, taken in March, 1925, when she was nine years old, is shown in figure 5. She was then 47 inches tall and weighed 48¾ pounds.

In November, 1918, almost eighteen months after she was first brought to the dispensary and found to be infected, she began to have eye trouble. Starting with phlyctenular conjunctivitis, this went on to keratitis with ulceration. When I saw her in 1923 she was suffering from chronic blepharitis, but in other respects physical examination was entirely negative. For the past two years her eyes have been clear.

FIG. 5. PATIENT JOSEPHINE L., PHOTOGRAPHED MARCH, 1925, WHEN NINE YEARS OLD

Although in continuous contact with tuberculosis since probably birth and known to be infected before one year of age, has had no symptoms of tuberculosis except chronic eye trouble (phlyctenular conjunctivitis, keratitis and blepharitis) from third to seventh years of age. Eyes clear for last two years. Continues to react vigorously to tuberculin. Present height, 47 inches, weight 48¾ pounds. See also figs. 4 and 6.

On March 19, 1923, roentgenograghy of her chest showed an enlarged mediastinal shadow which was interpreted as of tuberculous origin (see figure 6). Her skin reaction (Pirquet) was then exceptionally active. This high allergy continues up to the present time (March, 1925).

An X-ray of her brother's chest, also taken on March 19, 1923, is shown in figure 7. The same involvement of the mediastinum is also to be made out in his case. When the children of the family first came to the dispensary in 1917 this boy was five years old. He also reacted violently to tuberculin. In all the years that he has been under observation he has never shown the least

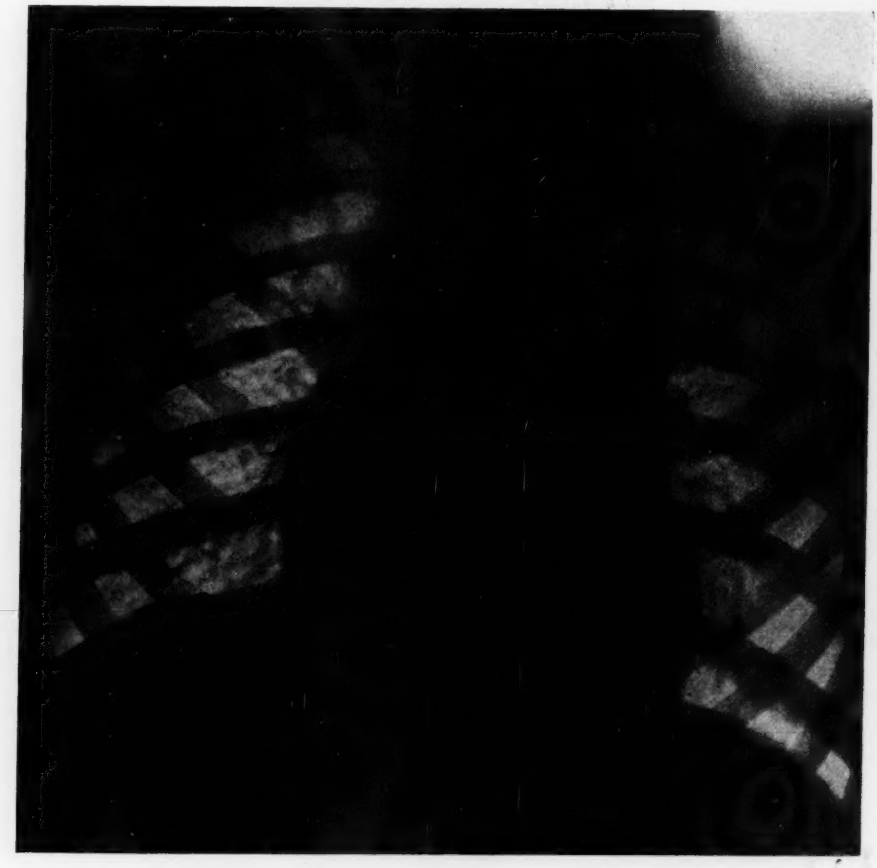

FIG. 6. PATIENT JOSEPHINE L., MARCH, 1923, WHEN SEVEN YEARS OLD

Mediastinal involvement. See also fig. 7

manifestation of tuberculosis, except that for the better part of a year, in 1918–1919, he had a marked enlargement of the deep cervical lymph node beneath he angle of the jaw (the so called "tonsil lymph node") on one side. This is no longer evident, and it is not known whether the swelling was due to tuberculosis. In March, 1925, he reacted vigorously to a Pirquet test.

Another brother was eleven years old when first seen in the dispensary in

1917. He also gave an excessive Pirquet reaction, although he was well at the time. In 1918 he had phlyctenular conjunctivitis, the only clinical tuberculous condition that he has shown. He left school early and has since been at work, and for this reason has passed from our observation for the last five or six years.

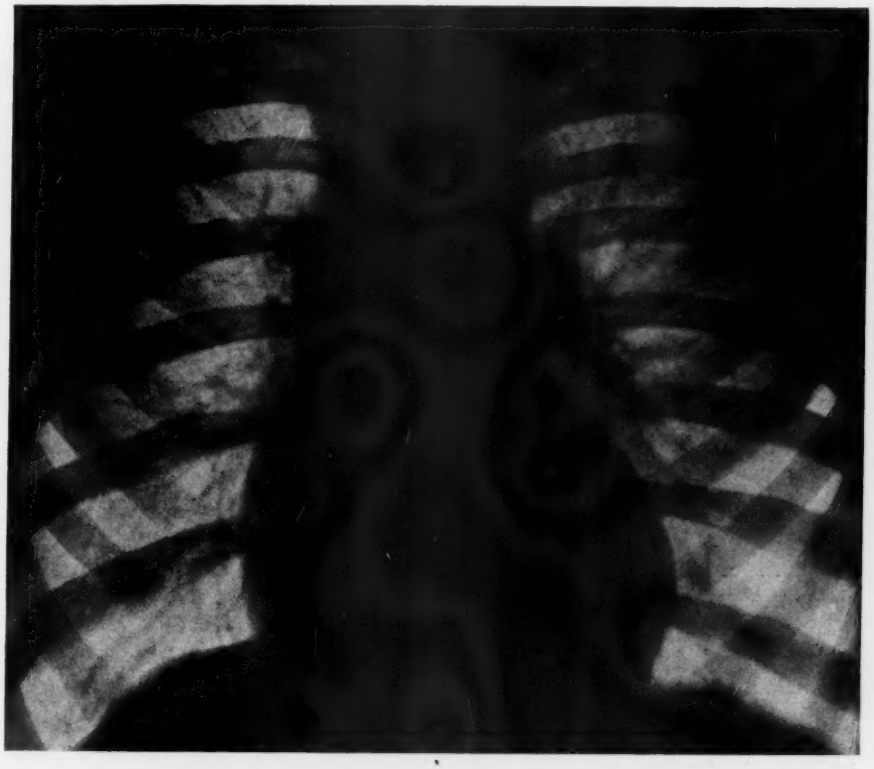

FIG. 7. PATIENT THOMAS L., BROTHER OF JOSEPHINE L., MARCH, 1923, WHEN ELEVEN YEARS OLD

Mediastinal involvement. See also fig. 6

In essentials, this little girl is not an exceptional case. She was infected at the age of one year or earlier; she has remained well and free from symptoms of tuberculosis except for chronic eye trouble which first appeared about eighteen months after she was known to be tuberculous and has since recurred; wherever the initial localization of her infection may have been, as years have gone on the infection has accrued at the lung root and it is here that it is now most manifest. What is rare in her case is the excessive allergy that she possessed in infancy.

Her father is still alive and continues to cough and spit blood; and after all these years of probably uninterrupted contact with tuberculosis the child is still highly sensitive to tuberculin though in no way comparable to her condition in 1917. Our experience has shown us that similar cases are common; that is, that many children, infected in the first few years of life, remain entirely well or merely have indefinite symptoms which, in ordinary practice, would elude correct diagnosis; that, wherever other evidences of infection may be, they will frequently be detectable at the hilum of the lung, usually without arousing symptoms; and that the hilum is commonly involved even though there be no *detectable* changes elsewhere. Infantile *infection* by no means involves the inevitable appearance of manifest tuberculosis in progressive or fatal form. As has been stated above the ratio of infantile tuberculosis morbidity and mortality to infantile tuberculous infection points out that in infancy, also, tuberculous infection is well-borne.

Reuben and Smith, writing in 1924, say:

> At present, the literature abounds with more favorable mortality statistics in tuberculosis in infancy. Oswald cites a mortality of 59.15 per cent in lung and bronchial gland tuberculosis. Frankenau, in observations on 40 children during second half of first year, gives a mortality of 60.3 per cent; and Fischl cites a mortality of 58.8 per cent. The prevailing opinion at present is that the prognosis of tuberculosis in infancy is not as grave as it was formerly thought.

However, it is doubtful whether the idea has "taken hold"; certainly, the gravity of tuberculous infection in infancy, and the alleged contrast between its hazards with those of adult infection, seem to be played up as much as ever.

In 1917, Hempelmann, questioning the soundness of the pessimistic view regarding infantile tuberculosis (10), wrote, "Actual studies of the fate of children infected with tuberculosis in infancy are extremely few." He then presented his own observations on the outcome of *pulmonary* tuberculosis in 130 infants under two years of age. His average mortality figure was 68 per cent, and some of the children were living after four or five years. Now, pulmonary tuberculosis is a serious type of the disease in infancy, and Hempelmann's findings suggest that, if babies can put up a moderately successful struggle against pulmonary tuberculosis, their reaction to tuberculous infection in general cannot be so unfavorable.

The proportion of sick and dead from tuberculosis to those infected is, nevertheless, much higher in infancy than it is throughout childhood; and this circumstance may be appealed to as an argument that infantile resistance to the infection is lower than later in life. Infants may, in truth, be *inherently* less resistant, but it will take more direct and positive relations than the figures of morbidity and mortality to prove them to be so. Indeed, altogether aside from any question of resistance, there is at least one first class reason, based on actual conditions, why a relatively large proportion of infected infants fall sick with tuberculosis and die of it. This is the undue opportunity for immoderately heavy infection that attends those infants that may be exposed to infection.

Every succeeding year after birth the sources of infection to which the infant and child are exposed increase numerically. It results, therefore, that the number of infected children in any age grouping is greater than the number at any earlier age. But the character of the exposure undergoes a great and often decisive alteration, if we contrast what must be the lot of numerous exposed infants with that of perhaps most exposed children.

For most infants infection must be brought to them, and exposure must take place in the home. It can hardly be otherwise than that the contact with tubercle bacilli will usually be consummated through the ingestion of contaminated cow's milk or through association with a phthisical member of the family. If it is through cow's milk the presumption is that the intake of bacilli will be frequent and large. What then saves many infants from fatal tuberculosis is the relatively low virulence of the bovine bacillus for human beings. It is not its "genius" to set up ulcerative pulmonary tuberculosis in man any more than it is within the capacity of the human bacillus to cause phthisis in cattle. Nevertheless, if the localization and further evolution of bovine infection are such as to allow the eruption of necrotic foci into large lymphatic trunks it can be scattered throughout the body and terminate in fatal meningitis and generalized miliary tuberculosis.

If contact with tuberculosis exists through a family relationship, the chances that it will be more intimate and quantitatively greater are much larger for infants than for older children. Infants have every want and necessity satisfied by one or two or, at the most, a very few persons. If the single attendant is phthisical, it will frequently turn out that practically every activity of the infant is touched by the human tubercle bacillus. Wherever there is a careless or unsuspected sufferer from tuber-

culosis in a home, it is certain that, in general, an infant in the domicile will be more heavily exposed to infection than will a child who is capable of self-locomotion and of self-help. If infected cow's milk comes into a home of infants and children, it will form almost the exclusive diet of the former and a diminishing part of that of the latter as these grow older. In this respect again the infant's opportunities for serious infection are greater.

From the age of two, three and four the child enlarges its outside sphere with an ever widening range. As it does so it will multiply its probable contacts with infection. It will meet more people and therefore increase its chances of falling in with one who suffers from tuberculosis. It will also attach to itself the sputum of the sidewalks, roadways and streets, that is deposited by the promiscuous expectoration of men of all types, well and ill; and some of the sputum may be tuberculous. Although their homes are free from cases of tuberculosis, active children outside the home will in these ways strike their first unconscious acquaintance with human tubercle bacilli. But these contacts are likely to be much slighter and much more transient than those that concern the infant in the "tuberculous" home or the older child in similar surroundings.

A vastly higher proportion of infected older children than of infected infants have suffered, no doubt, these milder exposures. We may be almost dogmatic on the general principle that, under the present conditions and habits of life within and without the home, more *exposed* infants than *exposed* children are in contact with gross and continuous infection.

This situation of itself goes far to explain why relatively many infected infants fall victims to tuberculosis. However much students may disagree on other points, they are unanimous in the opinion that, after a certain limit of tolerance is passed, the severity of tuberculous infection and its rapidity of progression increase with the numbers of virulent bacilli received and the frequency and diminishing intervals of their reception. Without any reference to differences of resistance, exceptional opportunities for infection fall the way of the exposed infant and are undoubtedly responsible for much of an effect that many would attribute to some inherent oversusceptibility of newborn tissues,—to a fertility of defenseless soil.

It is probably not any too well remembered that the man, who above all others laid the foundation of the doctrine of an adult immunity due

to tuberculous infection in early life, was inclined to regard an increased susceptibility of infants as *apparent* rather than real and as the resultant of unusual opportunities for infection. Roemer, experimenting with sheep, had failed to observe that newborn lambs are any less resistant to artificial infection than are fully grown animals: "a special predisposition to the disease could not be demonstrated in suckling lambs." He had also shown that in animals of the highest susceptibility, such as guinea pigs, an infection of protracted incubation period could be induced—"yes; this artificial infection could remain entirely latent for a not inconsiderable period"—if the proper "dosage" were employed in artificial infection. He therefore asks whether "it may not be that those human infants, who clinically or anatomically exhibit tuberculosis in the first or second year of life, suffer such severe infections because infections with massive doses are concerned." And he suggests that the peculiarities of infantile tuberculosis may be

> not the consequence of a special innate disposition to the disease, but the result of an infection that is grave, particularly as concerns its quantity. I say that in this way the alleged (*angeblich*) special behavior of infants toward tuberculous infection *can* be made understandable. As to whether this or another explanation is correct still requires much enlightening research (11).

It may be said that the trend of discovery,—of "enlightening research,"—since Roemer's day has been all toward Roemer's view. Since 1910 we have learned that nonmanifest, "latent" infection frequently occurs in infants, that a fair percentage of these subjects never become ill with tuberculosis, and that as manifest tuberculosis of infants becomes better recognized the proportion of recoveries increases. And all these facts must in time bring about a modification and revision of the still largely entertained idea of an exceptionally high inherent defenselessness of human infants to the onslaughts of tuberculosis.

The inordinate frequency of such fatal forms of the disease, as tuberculous meningitis and generalized miliary tuberculosis, in early life is frequently brought forward to illustrate the unique susceptibility of the infant to tuberculosis. Such evidence must be considered worthless until it can be shown that the affections mentioned are conditioned by abnormally low resistance. So far as the writer knows a relationship of this kind has never been demonstrated. The sole reason for regarding meningitis and generalized miliary disease as proceeding from a *status resistentiae minoris* has ever been the patent fact that both are among

the gravest issues of tuberculosis; and such ratiocination is simply a case of begging the question.

If resistance to tuberculosis is to be looked upon as a specific attribute of tissues, inherent in and peculiar to the components of some bodily organisms and lacking in those of others, or possessed in variable content and integrity by the individuals of a species,—and it is in some such vague and hazy implication that "resistance" is generally regarded,—then a fatal termination of tuberculosis by meningitis cannot be due to a failure of resistance. In the great majority of instances tuberculous meningitis (unassociated with generalized miliary tuberculosis) is lethal *by reason of location* of the pathological process. There is certainly nothing peculiar to the latter which, *of itself*, and *in its nature*, enhances its malignancy. Indeed, the pathological changes of tuberculous meningitis are frequently of such a kind—are so insignificant—that one may be positive that if they were situated at many other places of the body they would be insufficient to engender symptoms of illness. In other words, in case after case of tuberculous meningitis, the tissues of the individual react to tubercle bacilli with formations that would pass unnoticed if they originated in tissues other than the meninges of the same individual. So much must be self-evident, as must also be the circumstance that a "resistance" based on innate and *specific* ineffectiveness of tissue defenses has had nothing to do with the outcome.

As a matter of fact the tuberculous meningitis of infants occurs far more often as part of a generalized miliary tuberculosis than as meningitis alone. We must therefore ask for the evidence that would make generalized miliary disease result from a failure or lack of resistance. This has never been disclosed in the better-understood cases that occur among mankind. *In these, generalized miliary tuberculosis invariably takes place through the eruption of an already present tuberculous process into a channel that can send the seeds of infection to all parts of the body. And, as a corollary, it can be asserted with surety that if the very same process had been situated in any one of several other locations in the same body an identical happening (eruption of the focus) would have occasioned scarcely appreciable disease.* Surely this is not a result contingent on "resistance"—as resistance is generally understood.

One adult, one child, one baby, has an invested tuberculosis of the retroperitoneal lymph nodes, and keeps in health meanwhile: we may say that resistance is good, but we are talking in terms of appearances—we do not know a thing about resistance in the particular case. If

generalized miliary tuberculosis breaks out because the process ulcerates into the great lymphatic channels, we may say that resistance has failed—and be no doubt thoroughly wrong.

For another adult, another child, another baby, responds to not dissimilar tubercle bacilli, carried to its cervical lymph nodes, in a way that is no whit different from the unfortunate just mentioned. They keep well: their resistance (so we say) is also good—and we may or may not be correct. And if their tubercle ulcerates, they do not die. They do not even become very ill, and we, as a consequence, think little about resistance; or, at the lowest, we would rate it much higher than that of the patient dying with generalized miliary tuberculosis.

Yet, in terms of tissue reaction, of bodily resistance to tubercle bacilli, there has been no difference.

But we come back to the undeniable fact that by far the greater proportion of deaths from tuberculosis in infancy occur through generalized miliary tuberculosis,—an event that has generally found explanation in "lack of resistance,"—and ask for its reasons.

These quite likely reside in two factors: (1) the imperfect investment that must attend all young foci of tubercle and (2) the unusually favorable opportunities for the dissemination of infection in early life.

It is obvious that all tubercle of infancy must be of recent origin. Under the best conditions fibrosis is therefore likely to be incomplete, and not to be compared with that which would wall off the same foci several years later. Accordingly, the environmental forces accustomed to bring about the pathogenesis of tubercle—intercurrent disease especially, and perhaps malnutrition—will act much more effectively on the freshly laid down tubercle of infancy than on older formations. Questions of dosage of infection aside, given the proper environmental contributory factors coming into play in a tuberculous infant, the "opening up," or the eruption or extension of foci is peculiarly likely to occur.

And when it does occur there are at hand avenues of transport the structure of which makes widespread dissemination easier and more likely than at any other period of life. These, particularly as they are part of the lymphatic system, have been discussed fully earlier in this inquiry, and require no further comment here.

Therefore, by reason of anatomical peculiarities of normal structure and of pathological formations (tubercles) infants do, no doubt, stand in a special relation to tuberculous infection. In a certain sense we may

stretch our concepts of resistance to an infection, so as to bring within their province such anatomical peculiarities. Indeed, we have already done so when we laid down the thesis that from the point of view of lymphatic function the noninfected child (and infant) possesses less resistance to the advance of tuberculous infection than does the non-infected adult. But such a relationship postulates nothing concerning a specific attribute or defect which is almost invariably put forward to explain the different types of tuberculosis that are more or less typical of the several ages of man.

It is also probable that infants are to some degree inately (*but non-specifically*) deficient in one respect which tends to influence markedly the course of tuberculous infection. This concerns their ability to react fibrously to irritations and injuries of all kinds. The general response of infants with fibrous tissue would appear to be relatively weak, as may be observed in many infections and after wounds. This low capacity to form fibrous tissue is particularly noticeable during the first few months after birth.

Yet the proof of all these speculations and hypotheses lies in controlled experiment on susceptible animals. If susceptible mankind are natively more or less resistant to tuberculosis according as they are older or younger, then other susceptible species should, under the proper conditions, exhibit the same variations in degrees that are marked enough to be detectable. And the most enlightening commentary on the whole matter is that experiments have thus far either failed to disclose significant differences according to age or have resulted equivocally. The study which immediately follows this inquiry (12) represents another attempt to solve the problem with some exactitude, and adds one more to the list of failures to show that at different ages the members of a susceptible species vary in their *inherent and specific resistance* to tuberculous infection.

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APPENDIX A

REMARKS ON CONDITIONS NECESSARY TO AROUSE THE ALLERGIC STATE AND ON IMMUNITY THROUGH FIXATION OF BACTERIA

It was not until 1909 that we began to have systematic *experimental* studies on the allergic state, which comprehends the ability of animal *tissues* to react to specific antigens, under certain conditions, in an inflammatory manner. After Pirquet had discovered the cutaneous tuberculin reaction that bears his name it was found that tuberculous guinea pigs and rabbits, the ordinary animals of experiment in tuberculosis, would not react positively to tuberculin applied superficially to the skin *à la Pirquet.* But as soon as Moussu and Mantoux showed that tuberculous guinea pigs would regularly give splendid skin reactions to tuberculin injected intracutaneously (1), the way lay open to exhaustive studies on tissue allergy.

Their work prompted the well-known studies of Paul Roemer on hypersensitiveness to tuberculin, immunity to reinfection, etc., which have taken their place among the classics on these subjects. In his earliest paper (2) Roemer demonstrated a fact that for a long time was apparently not any too widely appreciated, namely, that a condition of tubercle set up in the animal body by *dead* tubercle bacilli in sufficiently large amounts will also give rise to skin allergy. At the time (1909) Baldwin was busy with his important experiments on anaphylaxis to tuberculoprotein, published in 1910 (3). While this exhaustive study dealt almost exclusively with general anaphylaxis as distinguished from tissue hypersensitiveness, Baldwin took occasion to per-

form intracutaneous tests after the appearance of Roemer's earlier papers. He confirmed the latter's statement as to the allergizing effect of dead bacilli, for in his work on anaphylaxis he reports and tabulates two guinea pigs made skin-sensitive by inoculations of dead bacilli in the form of T. R. Preliminary to investigating the possibility of sensitizing to tuberculin with nonspecific foreign-body tubercle, Baldwin (4) "injected a number of animals (guinea pigs) with various products of the tubercle bacillus and of tuberculous foci, but could obtain no positive reactions (of the skin) unless he produced tubercles by the inoculation of either living or dead bacilli." "If," said Baldwin, "tuberculin reactivity (skin) is present in any animal, the presence of tubercles in that animal may be predicated. The tubercles may be produced by dead, sterilized bacilli, and yet reactivity will be present, though less persistent than in an animal subject to a living infection."

In his Laennec Society address of 1911 (5) Krause summed up the conditions necessary for skin sensitiveness as follows: "At the Saranac Laboratory we have never been able to elicit a skin reaction in guinea pigs unless the animal has tubercles caused by living or dead bacilli; that is, a first injection of extracted protein will not sensitize to a later skin reaction." In numerous later papers this author repeatedly pointed out that the sole and only requisite for the state of tissue allergy is *anatomic* (histological also) tubercle, whether this be aroused by living or dead bacilli. A few years later Baldwin, in his Harvey Society Lecture (6), called attention to the same generalization. "Dead bacilli," he says, "will act temporarily in this way (that is, induce tissue hypersensitiveness) but pulverized preparations and extracts appear too fleeting in their effects to arouse it."

As to why a dead-bacillus sensitization is, *ceteris paribus*, milder and more transient than one produced by living bacilli, the answer undoubtedly lies in the relative vigor and permanence of anatomic effect of dead and living bacilli. When Roemer infected guinea pigs with varying dosages of the same living bacilli (7), he found that the intensity of the intracutaneous reactions varied directly with the extent and advance of the tuberculous process; in other words, at a given time after infection, animals infected with large doses of bacilli react more vigorously than those given small doses. Krause arrived at the same result, although he approached the problem in a different way (8). He found that guinea pigs inoculated with living bacilli of standard virulence reacted more strongly than those infected with bacilli of low virulence; and concluded, therefore, that cutaneous hypersensitiveness "varies directly with the extent and intensity of the disease," just as it "increases with progressive disease," "diminishes with the healing of the disease," and "is increased by reinfection." Quantitatively, therefore, it takes much larger doses of living bacilli of low virulence to bring about a degree of allergy comparable to that set

up by highly virulent bacilli, and still larger doses of dead bacilli to arrive at the same result. And, too, as far as lasting effects go, allergy from dead bacilli will diminish earlier than that from the same dosages of living bacilli of low virulence; yet in either instance a waning hypersensitiveness can be promptly whipped up by reinoculation.

We view allergy, therefore, as a deep-seated biological effect of specific tubercle, whatever may be the latter's origin. Any one who is familiar with the old and fundamental studies of Prudden and Hodenpyl (9) and of Babes and Proca (10) would predict that living and dead bacilli, applied correctly, must give rise to *essentially* the same immune effects of every kind. Prudden and Hodenpyl showed how the anatomic tubercle set up by dead bacilli is identical with the changes brought about by living tubercle. Babes and Proca demonstrated that animals, having received subcutaneous inoculations of dead tubercle bacilli, reacted to tuberculin with general, focal and local signs and symptoms. Classical experiments of many years ago, such as those of Straus and Gamaleia on dead bacilli (11), also occur to one. It is because of these and many other kindred investigations that might be mentioned (the literature of tuberculo-immunization with dead bacilli is very extensive) that we have long been accustomed to think of all effects of dead bacilli, whether these effects be anatomo-pathological, immunological or allergic, as not differing *in nature* from those of living bacilli. As for differences of degree and intensity, that is another matter, one that is contingent, on the one hand, on anatomic conditions that are static and retrogressive (as when dead bacilli are acting) and, on the other hand, on changes that tend to be progressive (as result from living bacilli).

For a number of years after the discovery of anaphylaxis and of tissue allergy, there was much confusion as to the relation of the two states. Standard textbooks on immunity almost invariably used the two terms interchangeably, implying that they denoted one and the same condition. That both are, at bottom, protein phenomena or the expressions of intoxication by protein or protein degradation products there can be little doubt. But from the very earliest studies those who worked in experimental tuberculosis have pointed out that, in tuberculosis, anaphylaxis and tissue allergy presented all the earmarks of possessing each a separate identity. Although I had several times previously called attention to the differences of basic conditions that attended the establishment of the anaphylactic state as distinct from the allergic state in tuberculosis, a growing misconception in articles on the subject led me in 1921 to summarize reasons for my belief that anaphylaxis and allergy are not identical and are not governed by the same mechanisms (12). I again quote them here, as in the original article, in italics:

a. Anaphylactic hypersensitiveness is easily and regularly established in an animal by the parenteric injection of dissociated tuberculoprotein. it is quite certain that allergy has as yet not been thus attained.

b. Anaphylactic hypersensitiveness to tuberculoprotein is very uniformly transmitted by inheritance through the female animal; no one has ever been able to record a similar transmission of tissue allergy.

c. Allergy to tuberculoprotein always comes into being through the establishment of focal tubercle, and in this way only; anaphylactic hypersensitiveness may or may not exist after the development of tubercle.

d. Unquestionably demonstrable immunity to tuberculous infection never accompanies anaphylactic hypersensitiveness in the nontuberculous animal, however high the hypersensitiveness may be; it always attends tissue allergy, no matter how low this is.

Accordingly, until new information to prove the contrary is forthcoming, it would appear that tissue allergy is a distinct phenomenon, having an identity all its own, and dependent on the presence of tubercle somewhere in the allergic body. One naturally asks why human beings, children for instance, might not be tissue-sensitized (skin) by dead bacilli which many presumably take in, since, as has been abundantly shown, dead bacilli confer allergy. Hypothetically, such a condition cannot be dismissed as impossible for human beings, but practically the contingency is open to grave doubt. As has been intimated above, a few, a very few living bacilli, if virulent, will produce tubercle that is moderately persistent and therefore capable of setting up moderately prolonged allergy: it is a matter of a few germs gaining access to the body and there maintaining themselves by multiplication. On the other hand, every one who has performed the experiment knows (as Roemer showed) that it takes relatively large doses of dead bacilli to allergize an animal *appreciably*. If allergy is to persist for years repeated large receptions of dead germs would presumably be necessary. We can hardly believe that those conditions exist in nature which will satisfy the requirements for appreciable and lasting allergy in human beings due to dead bacilli. In the requisite environment for this to happen a human being would also receive living tubercle bacilli.

The whole question is of a piece with the related one of active immunization with dead tubercle bacilli,—hypothetically probable but, as extensive experience has shown, quite faulty or altogether wanting for good effects in practice. It was so well put by Baldwin in his Harvey Society Lecture (6) that I cannot do better than quote him: "But we may again inquire, why is the living bacillus necessary (for immunity)? Cannot the dead bacillus persist a long time in the body and produce tubercles (as we know to be true)? If tuberculous tissue is needed why not use dead bacilli? The answer is

difficult, but it is not likely that the dead bacilli persist long (except when shut off in the form of encapsulated nodules where large clumps may lodge). The tissue changes are also probably less pronounced and certainly more transient."

As our knowledge of allergy has enlarged, we have been able to rewrite, in a way, the pathology, symptomatology and specific treatment of tuberculosis (12) (13) (14). But, by and large, its most important function is quite likely concerned with contributing to the specifically immune state. Vigor and great speed mark the reaction of the infected, and therefore the allergic and immune, animal to protein products of tubercle bacilli and to reinfections with bacilli themselves; whereas the nontuberculous, and therefore nonallergic and nonimmune, animals react not at all with tissue hypersensitiveness to dissociated derivatives of the germs, and only leisurely and tardily with tubercle to the living virulent bacilli. Moreover, the allergic reaction is inflammatory, while that of the nontuberculous animal to first infection is *primarily* proliferative.

When Koch described the *Koch phenomenon* (15), which we now recognize as a manifestation of high allergy, he believed that the animal concerned showed less tuberculosis upon reinfection because the reinfecting bacilli had been cast out with the slough that followed the allergic reaction. Later writers, such as Bezançon and deSerbonnes, have held a similar opinion (16). Rist and Rolland (17) thought that immunity is accomplished by lytic forces that accompany the inflammatory reaction of allergy. Baldwin (6) was inclined to take a similar point of view. Speaking of allergy, he said, "The inflammatory reaction following inoculations of immune animals is the prominent feature. . . . . Hence, we are justly entitled to the opinion that the cell accumulations about the bacilli are performing the duty of dissolving them or restricting their growth."

It is difficult to think of the effects of the allergic inflammatory reaction, brought to bear at places where reinfecting or metastasizing bacilli lodge, without falling back on some such concept as that lytic forces are set in play and cause the rapid disintegration and dissolution of the germs. Nevertheless, as I tried to put the case several years ago (18), "Direct scientific demonstration of these hypothetical lysins in tuberculosis has thus far been very incomplete and unsatisfactory. Personally, I cannot conceive of the allergic reaction going on without the intermediation of some kind of lytic action; yet I am disinclined to accept the lysin hypothesis without reserve and at its full face value until I can exhibit the lysins in a way that is free from criticism, and this I have thus far failed to do."

Yet the experimenter in reinfection will observe a phenomenon which casts doubt on the assumption that immunity to reinfection is accomplished by the

lytic destruction of bacilli during the play of the allergic reaction. The hypersensitive animal will accommodate, *for a long time* without *appreciable* metastasis (that is, anatomic change at places other than the site of reinfection), really astonishing quantities of reinfecting bacilli. It will similarly take care of small numbers of reinoculated bacilli for a still longer period. Yet, in either instance, it is the rule, and not the exception, that some bacilli of reinfection will survive, and in time appear in other parts of the body; and the outstanding result of the allergic (immune) reaction is *not the complete destruction of reinfecting bacilli but a retardation of their spread* (19), or normal development. Indeed, "it was because of this latter circumstance that Roemer, by reason of his own and Hamburger's observations, believed that in allergic animals the bacilli remained intact in tissues, yet deprived of their normal inherent power to act upon the latter (20)." If the allergic reaction exerts its influence through and by lysis, the end-effects of theformer are very puzzling indeed—for one asks, "Why do the lysins not destroy all bacilli? Why, even if dosage is small, are some bacilli usually left alive?"

Throughout fifteen years of work on hypersensitiveness no features of it have more closely and constantly engaged my attention than its rôle in immunity and the mechanism through which any protective effect of the allergic reaction may be accomplished. During the early years of our acquaintance with allergy the phenomena of immunity were viewed almost exclusively in terms of Ehrlich's elaborate structure. It was heresy to dream of tuberculo-immunization in any other terms than as an antigen-antibody tournament fought out in the blood-serum. It was really the allergic phenomenon that was first among immune reactions to defy being fitted into Ehrlich ideology. Yet to speak another language was to run the hazard of being unheard or uncomprehended. Nevertheless, as more and more work in tuberculosis immunology failed to disclose *toxins* and *antitoxins;* as, too, it became clear that *nontuberculous* animals could be made to yield serum "immune-bodies" though their resistance (immunity) to infection remained normal and unheightened, while *tuberculous* animals with no "immune-bodies" in their serum increased markedly in their resistance to reinfection as tubercle developed; as, again, it became plain that the same conditions underlay tuberculo-immunity and tuberculo-allergy, and that in acquiring allergy the activity of the cells of the body became profoundly modified, I at last (in 1916) made bold enough to publish a short note on *Cellular or Tissue Immunity to Tuberculosis*, etc. (21), a theme which in the following year I developed at greater length in a lecture on *The Nature of Resistance to Tuberculosis* (22).

In my note of 1916 (21) I mentioned how two citations (of work of Pawlowsky and Issayeff) by Opie in his Harvey Society Lecture on *Inflammation* (23) had suggested to me the possibility that specific immunity to reinfection in tuberculosis was a function of allergy, in that the inflammation accompany-

ing the latter prevented the spread of reinfecting bacilli; and in my lecture of the next year (22) I put the case more concretely as one in which "the tuberculous animal responds with exaggerated or overreaction to irritation and throws up a barrier against the bacilli much more actively than normally and before the bacilli can get under way."

Opie had said that "Pawlowsky had demonstrated the presence of staphylococci in the blood and organs of guinea pigs from twenty-four to forty-eight hours after inoculation of the knee-joint, but has been able to show that this dissemination is inhibited or wholly prevented if, before inoculation, acute inflammation of the joint has been produced by the injection of some sterile irritant such as turpentine, alcohol or solution of quinine. . . . . Issayeff . . . . showed that the peritonitis induced by a variety of sterile irritants, such as foreign blood-serum, bouillon or normal salt solution, temporarily increased resistance to subsequent intraperitoneal inoculations of bacteria."

These observations led me to attempt to prove experimentally the arresting or fixing effect of inflammation on tubercle bacilli—inflammation *as such* and without any reference to its origin. At the Saranac Laboratory, between 1910 and 1913, I tried to induce with nonspecific irritants inflammations of the skin (in nontuberculous guinea pigs) which would resemble the inflammation of the tuberculin reaction, with the further object of inoculating virulent tubercle bacilli into such patches of acute inflammation and observing the rate of spread of the bacilli from the sites of inoculation. In order to meet possible criticisms that I might be using bactericidal and therefore sterilizing agents. I purposely refrained from applying such chemicals as alcohol, turpentine, etc., to set up a nonspecific inflammation, but worked with other irritants—heat, bruising, needling, mustard, cantharides, etc. These experiments failed because none of the irritants used produced an inflammation which physically and quantitatively was comparable to that of the allergic reaction. Because of their failure the experiments were never reported in detail but, a number of years later (in 1920), they were cited in a paper by Krause and Willis (24).

While all of the studies cited, and especially those by Krause and Peters (20) and Krause and Willis (24), pointed to the soundness of the working hypothesis that, through the allergic reaction, the allergic state set up a series of tissue activities which operated *mechanically* to fix tubercle bacilli at points of infection and thus prevent or retard their spread, they did not bring forward the direct scientific proof that this fixation actually occurred. Accordingly, work was begun to demonstrate, as a fact, the fixation of tubercle bacilli of reinfection in the tuberculous (allergic) animal.

It was first necessary to know by what paths and how rapidly tubercle bacilli are transported from sites of inoculation in normal animals (guinea pigs) of first infection. This inquiry was made, and its results were reported in 1920 (25). Since then similar studies on the rate of dissemination of tuber-

cle bacilli in immune animals have been made by Krause and Willis. Only a summary outline of them has thus far been published (19) (26). They were in progress for about five years and a full report is about to go to press; but a summary of conclusions may be quoted from a recent *Bulletin de l'Union Internationale contre la Tuberculose:*

1. In normal nonimmune guinea pigs tubercle bacilli, inoculated intracutaneously or subcutaneously, are carried almost immediately (within an hour) from the portal of entry by the lymphatics.
2. Within three or four days they have made the circuit of the body.
3. In immune (allergic) animals their transmission is greatly retarded.
4. They remain fixed at or near the portal of entry for about seven days.
5. They do not reach the regional lymph nodes (superficial inguinal and axillary) until two weeks after infection.
6. They do not become generalized throughout the body until three or four weeks after infection.

We believe, therefore, that specific tuberculo-immunity occurs through a fixation of germs that results from the operation of the allergic reaction. An almost immediate inflammatory outpouring hems in the bacilli more or less effectively and thus delays or prevents their spread which is so facile and rapid in the nontuberculous, nonallergic animal. Associated with this early inflammation in the allergic animal is also a tendency to the accelerated development of proliferative tubercle (20) which also helps to bar the dissemination of germs. Nevertheless, exhaustive study will show that, unless bacilli are few, the check to their transportation is probably never complete, sufficient though it be to delay greatly or even prevent altogether the later development of significant foci elsewhere in the body. "The immune state (that is, the allergic reaction) operates to retard the spread of the bacilli from the portal of entry rather than to inhibit completely their activities or their multiplication" (19).

This conception of the fixation of bacteria (tubercle bacilli) through the allergic reaction has gained in point and plausibility since the appearance of a recent work by Opie (27). We quote from his conclusions:

When proteins such as horse serum or crystalline egg albumin . . . . are introduced into a normal animal they diffuse widely in the tissue, enter the blood stream, and are desseminated throughout the body. The same substances introduced into an immune animal are fixed at the site of entry and are not found in the blood.

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APPENDIX B

REMARKS ON THE HEALING AS WELL AS ON THE LONG CONTINUANCE OF FOCI OF REINFECTION

Trudeau was undoubtedly one of the first to observe and grasp the fact that foci of reinfection heal. In the paper of 1903, already cited (footnote 3 of the text), *Artificial Immunity in Experimental Tuberculosis, New York M. J., July 18, 1903*), while speaking of the lesion that results from the reinfection of rabbits, he says, "In the protected animals, however, the process, both in the eyes and lungs, gradually becomes retrogressive and heals slowly without any tendency to spread. In other words, there is in them a reaction, but one that is purely localized; while in the unprotected rabbits the disease steadily progresses and becomes generalized until it destroys the animal's life."

At another place in the same paper he remarks, "The immunity is shown by the fact that the lesions so rapidly produced tend in the protected animal to remain localized and to retrograde and *become absorbed.*" (Italics A. K. K.'s)

I have recently described this process in greater detail (Discussion of paper, *The Absorption of Pulmonary Deposits,* by J. Burns Amberson, Jr., *Trans. Amer. Climatol. & Clin. Assoc.*, 1924, xl, 182), as follows:

> In experiments on tuberculosis immunity we find the most remarkable disappearance of tuberculous changes—of tuberculous pneumonia and of tubercle that has caseated. We may immunize rabbits by giving them an initial infection with proper amounts of human tubercle bacilli. Several weeks later we may then reinfect these animals with quantities of bovine bacilli, which, also applied at the time to control rabbits, will bring about in the latter progressive infection and, after several months, death. The reinfected animals will, however, display their high immunity to the bovine infection by living for many months—perhaps for several years.
>
> If we kill such animals—both those of bovine-bacillus reinfection and those of bovine-bacillus infection as a first infection—in series and at various intervals, then we shall find that the immunity of the former does not appear as a complete or partial warding off of bovine bacilli *at the time of bovine infection,* but is displayed in overcoming the bovine tuberculosis after a good deal of it has developed. For instance, four weeks after bovine infection both immune and nonimmune animals will have markedly involved lungs and in both series there

will be some caseation. At this stage a person without knowledge of the antecedent histories of the animals could hardly tell the difference between members of the two series.

But, from this time on, the difference of evolution of the infection in the two lots will mark each off from the other. All the nonimmunes will get more and more tuberculosis, and worse and worse pathological changes, to succumb within several months. But if we continue to kill the immune survivors at intervals we will find less and less tuberculosis in them; until, after nearly a year, we find only an occasional discrete tubercle in their lungs, with completely normal lung tissue between. And we can come to no other conclusion than that where once there had been massive tuberculosis, with not a little caseation, there occurs, in time, a healing of tuberculous changes, a disappearance of these, and a restitution of much of the lung to normal.

At the same time experimenters of large experience become familiar with foci of reinfection that do not heal completely; foci which, while remaining localized or, at the most, spreading slowly, pursue a chronic and long-drawn-out course. If an allergic (infected) animal be given very small quantities of bacilli by way of reinfection, the resulting acute exudative process is likely to subside with fair rapidity (in several weeks), and disappear. If excessive numbers of reinfecting bacilli are acting, the animal runs the risk of being overwhelmed by the violent and extensive tissue changes and, as commonly as not, will die within a few days after reinfection; if it recovers from its acute illness, it will proceed to resist the reinfection immeasurably better than will an animal given the same inoculation as a first infection. Whatever clinicians or pathologists may say about such fulminant effects of tubercle bacilli being due to bodily *nonresistance*, it is indubitable that they are the expressions of immunity. Experiment proves unerringly that *only the specifically immune animal reacts vigorously (acutely and exudatively) to tubercle bacilli.*

But very frequently, if reinfecting "dosage" has been moderate, the result will be foci of long duration,—of months. Such foci usually ulcerate, as may be observed by making inoculations into the skin, and the ulceration may keep up for a long ime. An observer of this very common occurrence cannot help believing that similar ulcerated foci of reinfection, if situated in the human lung, would there encounter conditions suitable to have them set up manifest or active clinical tuberculosis.

All this, of course, squares with a point of view that dates back to Roemer and is at present being advocated by Opie,—that discrete and chronic pulmonary foci (so typical of adult tuberculosis) are reinfection foci because of their chronicity. The idea is no doubt correct as regards many, though by no means all cases. At the same time, one should keep in mind that, even though (for argument's sake) it were granted that every chronic adult focus of the lungs originated as a reinfection in allergic soil, neither its character or location prove anything regarding the source of the reinfection. A new infection from an anterior process (metastasis) will set up a formation that is no different from that aroused by superinfection from without. If the chronic focus is

chronic because of the body's immunity, the presence of the anterior focus (with living bacilli) at the time of reinfection is postulated, and is a necessary condition to the event. If such an anterior focus existed it has within it always the capability and possibility of sowing the seeds of daughter foci—that is, foci of reinfection.

AN EXPERIMENTAL STUDY OF THE COMPARATIVE RESISTANCE OF YOUNG AND OLD GUINEA PIGS TO TUBERCULOSIS[1,2]

ALLEN K. KRAUSE

Few opinions regarding tuberculosis are more widely held than that of a relatively low resistance on the part of young animals, particularly the young of the human species, to the infection. The matter of the resistance of the several ages of man to tuberculosis has received attention in a paper that accompanies this one and immediately precedes it (1). The idea that the young of susceptible species are less resistant than the mature can hardly be said to rest on published experimental evidence. Not long ago Bender and DeWitt called attention to the paucity of authentic information of this nature. In a study of the elements of the circulating blood in experimental tuberculosis (2) they found a normal condition of high lymphocyte content in newborn guinea pigs. They considered it difficult to square their observations of lymphocytic relations with the part that a number of authors ascribe to the lymphocyte in the production and operation of resistance and immunity to tuberculosis. As they put it:

> The guinea pig, like the human infant, has a very high percentage of lymphocytes and a relatively low resistance to tuberculous infection. It would be worth while to determine the resistance of the newborn guinea pig, which has a low lymphocyte count similar to that of the human adult. This has apparently not been done.

As a matter of fact, there have been a few studies on the subject, none of which can be said to be very sufficient or satisfactory. A recent paper by Kleinschmidt cites most of these and to this the reader may be referred for a brief summary of the literature. Kleinschmidt's own study is a report of the results of inoculation of two series of guinea pigs with tubercle bacilli. In the one series are tabulated three newborn and two

[1] From the Kenneth Dows Tuberculosis Research Fund of the Medical Clinic of the Johns Hopkins Hospital and University.

[2] Presented in abstract at the annual meeting of the American Climatological and Clinical Association, Atlantic City, New Jersey, May 1, 1924.

adult guinea pigs; in the other, five newborn and four adult guinea pigs; although the author states that "two further experiments (not tabulated) disclosed nothing essentially new." Obviously, a few more than a score of guinea pigs can hardly be expected to afford compelling evidence in an experiment that, by nature, obtrudes with variables. Kleinschmidt's citation of previous studies leaves one with the leading impression that what little work has been done has been equivocal and conflictng. One investigator, Wakushima, came to the conclusion that guinea pigs are *more* resistant to tuberculosis when newly born than at any other period of their lives.

Because paper after paper, of those appearing on many subjects in tuberculosis, avers that young animals are, in general, inordinately susceptible to tuberculosis and because many an author easily and lightly solves a knotty problem, as it arises, with a statement of the assumption, it is particularly desirable to point out on how slender a basis of ascertained fact the assumption is based. Indeed, it was the frequent recurrence of the statement in the literature, unwarranted as it seems to the author, that led him to undertake the present study, a controlled investigation of the relative susceptibility (or resistance) of young and adult guinea pigs to tuberculous infection.

Two experiments were accordingly performed. In the first, all animals were inoculated intracutaneously; in the second, subcutaneously. The first experiment afforded the opportunity to record the appearance and continuous evolution of all foci of inoculation, as these were always accessible to observation, and to note whatever differences might develop. In the second experiment the early detectable changes were the enlargement of those lymph nodes regional to the sites of inoculation, enlargements that first become noticeable in the second or third week after infection.

Our methods of estimating or measuring the relative resistance of any series of guinea pigs to experimental tuberculosis are at best very coarse. If the conditions of infection of a large number are the same and if, during the course of infection, the environment of the animals as regards caging, feeding, etc., remains the same, there exist several signs, of variable worth, of the progress of infection. Best of all is the notation and comparison of the visible tuberculosis at any given and definite time after infection. This involves the killing and general autopsy of whatever animals are under observation. It is the only procedure that is reasonably satisfactory, for in every animal it discloses how far infection

has spread and how extensive it has become within a stated time after the reception of bacilli; and extent, location and character of tuberculous changes constitute the only unequivocal evidence of resistance obtainable in experimental animals. Duration of life after infection may tell us something as regards the potency of infection. Frequently it is in accord with the pathological changes of the tuberculosis. But frequently it is not; and autopsy makes plain that death has been caused by some condition other than tuberculosis; that, as may happen, death has overtaken an animal that manifestly has been resisting tuberculosis well. The increasingly frequent occurrence of respiratory and enteric nontuberculous diseases among caged guinea pigs, especially in winter when most laboratory work is carried on, and the undoubtedly incompetent and insufficient care that characterizes the keeping of guinea pigs in not a few laboratories weaken seriously the value of such evidence as differences in duration of life indicating differences of resistance to tuberculosis. Tuberculosis is a chronic and prolonged infection, as such things go, even for guinea pigs, and in the several months of its course these experimental animals may be subjected to a number of influences that shorten life, altogether apart from the effects of tuberculosis. For these and other reasons duration of life, *of itself*, is no evidence of an animal's resistance to tuberculosis; it must in every case be associated with complete pathological information and the assurance that particular animals or cages have not been unduly well or poorly cared for. Of course, if the generality of a series dies soon after infection, with much tuberculosis, while that of a related series dies long afterward, with much tuberculosis, the difference in time of survival has its weight in forming an opinion as to resistance. But, when conditions of infection are similar, this is the quite unusual result. What ordinarily happens (and then, as a rule, when infections are heavy) is that differences of length of life are relatively slight and quite irregular; so that it is seldom that the trained and unprejudiced observer does not feel that they fall well within the limits of error—of expected and unavoidable variables—of the experiment.

In accounts of tuberculosis experiments nothing is more common than to cite fluctuations of weights of animals after infection as evidence of the progress of the infection. If guinea pigs are given overwhelming inoculations they may lose weight early and gain little or not at all later, even though kept under the best conditions. But significant and trustworthy experiments on resistance in guinea pigs are obviously not to be made with overwhelming inoculations; for these bring about a condition

of rapid and extreme infection that blots out or obscures any variations of resistance that may exist. In studies of this nature, what one wishes to obtain is a sufficient infection,—one that will spread in an orderly and sequential manner in the control animals until it at last becomes generalized and causes death within several months. With such a condition as a basis of comparison, one may then note variations from it as these occur in "test" animals.

With infections of this kind it has always been our experience that practically no animals lose weight, until very late in the disease, and that it is the general thing for them to gain even while the infection spreads to all parts of the body. Our laboratory does not inoculate guinea pigs until they have been in residence for at least a preliminary week or two, during which, as they become accustomed to their new environment, they are weighed and watched, and those that seem below par are discarded. This preinfection care, together with our routine methods of liberal feeding and scrupulous cleanliness, has resulted in an exceptionally low mortality from causes other than tuberculosis. Weeks may elapse without losing a single guinea pig out of hundreds, and we are accustomed to carry many animals through two, three and even four years. We feel that measures of feeding, caging and general care, as we have worked them out, are of the greatest importance in conducting any infection experiment. With these in vogue we observe no loss of weight except when there is extreme or rapidly progressing tuberculosis.

Nevertheless, in the present experiments, we took the opportunity to record systematically the weights of almost 150 guinea pigs, of marked contrast in age and size, throughout the course of progressive tuberculosis. By way of comparison, we also kept under identical living conditions ten young guinea pigs of the same original stock but not subjected to experimental infection. Beginning from six to twelve days before infection and continuing throughout the duration of the first experiment, weighings were made frequently,—sometimes as often as twice a week. There would be periods, of a few days or a week, when weights remained stationary or declined a little, but at these times all animals would be similarly affected, that is, the cage of nontuberculous controls would show the same general trend as the inoculated animals. This circumstance showed clearly that some general influence, apart from the tuberculosis, exerted an effect on the animals' nutrition, and that the infection was not alone responsible for these declines in weight or failures to gain.

It might be expected that young animals, infected during the height

of a period of normally rapid and vigorous growth, would gain in weight, even though laboring under progressive tuberculosis. We anticipated this. But we were not prepared to find large and fully grown guinea pigs make substantial increases while tuberculosis was spreading; yet this happened in a number of instances.

In the first experiment in which weights were most frequently and carefully recorded, there were 34 young guinea pigs that survived. On the day of infection their average weight was 237 gm. Eleven weeks later, when all were found to have generalized tuberculosis, their average weight was 392 gm. Their average gain was, therefore, 155 gm., or 65 per cent. Against these may be set 9 young guinea pigs, which were not infected, but belonged to the same stock as the preceding animals and were carried through as controls on general animal-room conditions. Their average weight when the experiment was begun was 250 gm.; at the close it was 440 gm., a gain of 190 gm., or 76 per cent. The average weight of 26 survivors of the old infected animals of this experiment was 596 gm. on the day of infection. At the end of the experiment, eleven weeks later, it was 647 gm., a gain of 51 gm., or 9 per cent. A few of the old animals were exceptionally large when infected, yet continued to gain in weight throughout. For instance, one weighed 830 gm. on the day of infection and 882 gm. eleven weeks later when found to have generalized tuberculosis; another weighed 710 gm. at the beginning and 757 gm. at the end of the experiment; a third, 657 gm. at the beginning and 802 gm. at the end.

We do not cite these records of weights in order to maintain that tuberculosis has no effect on the nutrition of guinea pigs under experimentation. It is quite likely that it may have a retarding influence in every case in which it is active. This probability is indicated by the fact that over 34 infected young guinea pigs, weighing 237 gm., on the average, to begin with, gained 65 per cent while 9 noninfected controls, weighing 250 gm. at first, increased their weight 76 per cent under similar conditions of environment; for this circumstance is contrary to the rule that normally the rate of gain in weight of animals is inversely proportional to their initial weights.

The point is that good gains in weight are compatible with advancing tuberculosis in guinea pigs and that, ordinarily, fluctuations in weight may be unsatisfactory or worthless guides of the state of the infection or, therefore, the "resistance" of the animals. This is, of course, anything but new information to seasoned experimenters in tuberculosis. It is

again presented here, and dealt with at some length, because a contrary statement or implication is still so frequently a feature of studies on experimental tuberculosis and because the present investigations provided excellent opportunities to renew controlled observations on the subject in animals of diverse sizes and ages.

In the two experiments to be related the young animals involved were not newly born. The principal reason for not using such guinea pigs was that the difficulties of controlling their environmental conditions bade fair to be so great as to endanger any interpretations that might have been put upon the results of the experiments. In studies of this nature comparisons of effects have value in proportion as the conditions of the experiment are simplified and tend to be similar. It is unquestionable that environmental factors exercise a marked influence on the course of tuberculosis. It can hardly be gainsaid that, with everything else equal, tuberculous infections will be likely to take a more unfavorable course, to progress further and more rapidly, in animals that are not so well adjusted to their surroundings than in those that are better accustomed to them. Animals gain in their adaptation to cage-life as time elapses from birth and, as time passes, thus become "stabilized." Altogether apart from the question of their manner of reaction to any infection, the general metabolism and vigor of caged guinea pigs will be much better, much more normal for caged guinea pigs, several weeks after birth than during the first few days after birth. It must be remembered also that the course of an artificial tuberculous infection runs several months, and that infection in newly born guinea pigs would be one that was becoming established while the recipients were laboring under the handicap of striking a balance with whatever environment they were destined to live in. At any rate it would be a handicap for them if they were to bear comparison with animals that had become "stabilized" for a longer time. And, if tenable relations are to be formulated in respect to the inherent capacity of several sets of animals to withstand tuberculous infection, an almost absolute requirement of the experiment must be that all animals go into the experiment with their bodily powers functioning, not only as nearly normally as possible, but also as nearly alike as possible.

There can be few laboratories in a position to breed their own guinea pigs in sufficient numbers, so as to have enough animals born at the same time and thus be available at the same time, as newly born guinea pigs,

for an experiment of this nature. The animals must, therefore, be born at some other place and removed thence to the laboratory. This transference at once would involve hazards and stresses, which, together with the radical change of environment, would tend to debilitate temporarily the animals, and the more so as they happened to be younger and weaker. It is obvious that no "newly born" guinea pigs should be inoculated immediately with tubercle bacilli under such conditions; certainly not, if they are to be compared with much hardier full-grown stock. At the very least, a week or two in new surroundings should be allowed to pass before they were subjected to infection. Under such circumstances the guinea pigs, when infected, would no longer be "newly born," as we understand the term as used in a communication or two on the subject.

It was to do away, as much as possible, with interfering factors of the above nature that, in the following experiments, we did not use newly born animals. Nevertheless, the younger members of the series were immature, physically and sexually, while the older ones had long attained full development. All the young guinea pigs were four weeks old when they reached the laboratory, where they were kept for from six to twelve days before infection. They were thus four or six weeks old when inoculated. All old guinea pigs were over six months old when they arrived (many were much older) and were also kept six to twelve days before being infected. All animals, both young and old, in each experiment, came from the same stock and the same place, arrived at the laboratory at the same time and were inoculated at the same time.

EXPERIMENT 1

In this experiment inoculation was *intracutaneous* in the side, performed October 3, 1923. The experiment was terminated December 19, 1923, by killing all survivors and noting the autopsy findings. The duration of the infection was therefore 77 days.

The *inoculated animals* comprised 37 young and 29 old guinea pigs, of which 34 young and 26 old lived throughout the period of the experiment. The young varied in weight from 165 to 292 gm., although only 10 were over 250 gm. and, as mentioned above, the average weight was 237 gm. The old varied from 457 to 830 gm., although only one of them was below 480 and 9 below 500 gm., and their average weight was 596 gm.

The *strain of tubercle bacillus used* was the well known Saranac Laboratory H37, of human type. The *inoculum* in every case was 0.1 cc. of a suspension (physiological salt solution) that was practically free from clumps and contained an average of one to two bacilli per oil-immersion field. The suspension had been prepared with great pains, as it had been centrifugated for 10 minutes

at high speed and then several times filtered through cotton and further diluted until the desired medium, containing few bacilli, and these single and isolated, was obtained. *In this experiment, therefore, infection was performed with relatively small numbers of tubercle bacilli.*

Course and Result of Experiment: Soon after infection very distinct and, indeed, striking differences appeared between the young and old animals. These concerned the time of first appearance of the lesions of inoculation and the rapidity and extent of development of these, as well as the changes that involved the superficial inguinal lymph nodes draining the foci of inoculation.

There was, in general, earlier visible reaction in the old animals, as well as a more marked progression of the foci of infection. The same greater rapidity and evolution of infection affected also the lymph nodes in the old guinea pigs. On the ninth day after infection most young animals showed only the slightest nodule appearing at the site of inoculation, while in many there was no noticeable change whatever. In the old animals, however, the local reactions were, with four exceptions, marked. The recorded notes for the day read "universally much more marked local reaction" in the old and "the difference is very striking." At the same time there was no suggestion of lymph-node changes in any young animal, while among the old there were a number in which the nodes were recorded as already "shotty."

By the twelfth day the tuberculous changes had progressed greatly, so that now the differences between the two sets of animals were much more marked. Practically all the young guinea pigs now showed some nodular formation at the site of inoculation; but in every case this was much slighter than in the old animals (fig. 1). In many of the latter the nodules had broken through and become already scabbed,—a rare occurrence in the young. Among the old guinea pigs lymph-node enlargement was very general and in some of these quite marked, while in the young it was still almost absent at this time.

In the accompanying figure 1 are shown the local changes in two representative animals of each lot twelve days after infection. The drawings portray accurately the much greater development of lesion in the old guinea pigs at this time. The same degree of difference existed without exception between the members of the two series.

While the inoculations were being made one became aware of difference in the texture of the skin of the two sets of animals. The skin of the older animals offered considerable resistance to the entrance of the

needle of the syringe and required considerable pressure to force the suspension of bacilli into and between the layers of the *cutis*. The injected suspension which caused a bleb was then absorbed only slowly. In the young animals, on the other hand, inoculation was easy and free, the suspension entered under only slight pressure, and the bleb subsided rapidly.

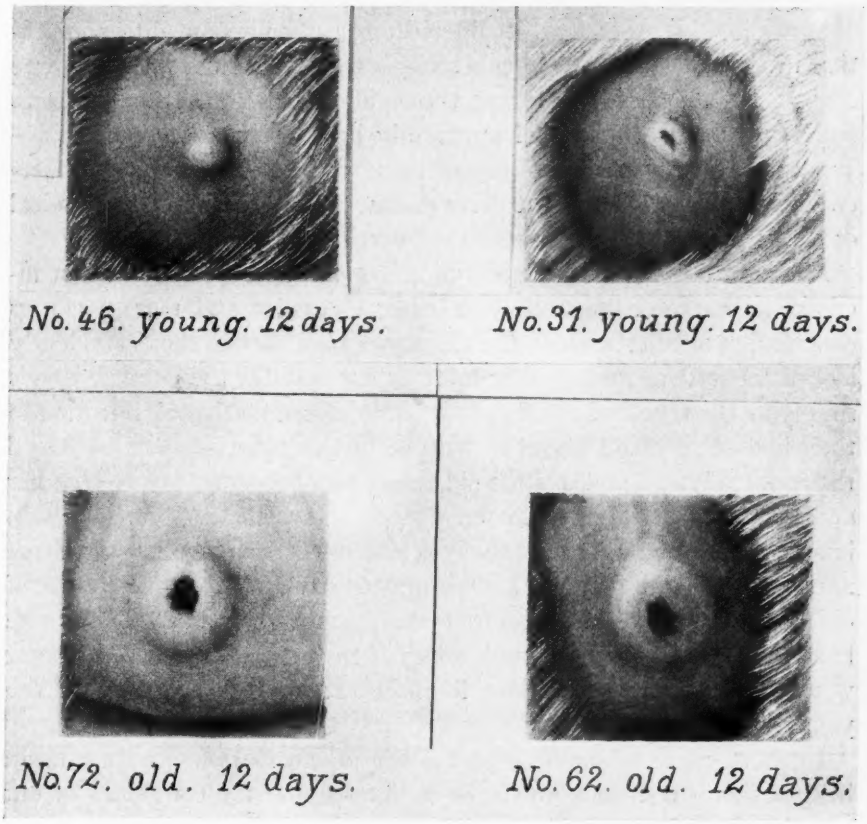

FIG. 1: INTRACUTANEOUS INFECTIONS OF YOUNG AND OLD GUINEA PIGS WITH SAME DOSES OF LIVING VIRULENT TUBERCLE BACILLI

All drawings were made at the same time, 12 days after infection. Note the more advanced changes in the old animals.

It was evident that, as was to be expected, the skin of the old guinea pigs was thicker and quite compact, and that of the young animals thin and comparatively loose or open in structure. In the latter, therefore, one would expect a relatively free and rapid dissemination of bacilli away from the points of inoculation, while in the old animals one might predict the confinement or fixing of more bacilli at these points. If this actually

happened then one could reasonably attribute an earlier and more pronounced development of inoculation tubercle in the old animals to the larger depots of infection that would remain at the points of inoculation. With more bacilli fixed at these points there would remain fewer of the initial bacilli to be carried at once and rapidly along to the interior of the body. Tuberculous infection gains in progressiveness and gravity as it is capable of spreading. If, therefore, it suffered any early impediment or limitation in the old animals, less tuberculosis throughout the body at large could be looked for ultimately in these guinea pigs. What we ought to find would be a condition of apparently better resistance in the old—apparently better resistance because there would be less extensive tuberculosis, although this less extensive disease was the result of mechanical obstacles and checks to metastasis of infection.

It was in terms something like the foregoing that we were at first inclined to interpret the totally unexpected earlier and more vigorous evolution of local tubercle in the old guinea pigs, and we then confidently looked forward to finding later more tuberculosis in the young animals simply as the result of a more ready early dissemination of infection in their bodies. But we began to weaken in this opinion when we found the regional lymph nodes of the old guinea pigs becoming involved earlier and to greater effect than in the young. Nevertheless, we could still imagine that since, as is true, the lymph nodes of young guinea pigs have normally a much more open and permeable structure than have those of old guinea pigs, these also allowed the passage through of many more bacilli than "got by" the lymph nodes of the latter; and that this event would again be reflected later in more extensive tuberculosis in the young.

In short, more tuberculosis at the site of inoculation need not mean less (or more) resistance to the infection. Under the conditions of our experiment it occurred in the old animals because more bacilli of the original infection remained there, and nearby (in the regional lymph nodes), to set up pathological changes. More local tuberculosis would quite likely be found to be accompanied by less generalized tuberculosis—and, therefore, what might superficially be termed a higher resistance—because fewer bacilli could be carried to the internal organs. Such was our view of the early developments of the experiment.

As time went on the differences between the young and old animals became still more marked. A transcript of the notes made on the sixteenth day after inoculation reads:

In general: Infection at sites of inoculation and in regional lymph nodes is now well established and progressing rapidly. The advance within the last few days is striking and significant. This—after 12 to 14 days—seems to be the period of marked reaction to the infection. Is it a matter of the establishment of hypersensitiveness?

Young animals: All, practically, gaining weight; ulceration of sites of inoculation occurring; regional lymph-node enlargement setting in.

Old animals: Most gaining weight; ulceration well over with, and deep pitting and scarring taking place; regional lymph nodes becoming enormous.

Differences: Both sites of inoculation and lymph nodes much further along in old than in young. Differences more marked now than at any time so far.

On the twenty-second day observations were essentially similar to those made at sixteen days. The infection was still progressing in both young and old guinea pigs. With one or two exceptions ulceration had now occurred in all animals, to leave a scabbed, umbilicated formation. The regional lymph nodes in the old animals were all much larger than in the young, and in some had now become enormous, knotted masses. Very few animals of either lot were losing weight; slow to good gains were still occurring.

On the thirty-sixth day it was noted that all animals had gained in weight. The marked gains were in the young. Lymph-node changes during the last two weeks had been slight and unimportant. If one compared the weight changes among the tuberculous young animals, that occurred between the thirtieth and thirty-sixth days, with the changes among the normal, nontuberculous controls for the same period, one noted no difference. This is graphically brought out by setting in parallel columns the weights of the members of the cage of normal guinea pigs and those of a cage of tuberculous guinea pigs on the two days mentioned (table 1).

After the fifth or sixth week nothing new or noteworthy developed among the animals. They were in a state of slowly progressing tuberculosis (as an occasional death and autopsy would show) which ran an uneventful course. Successive observations always noted that, in general, weight was gained from week to week. On the seventy-seventh day, or exactly eleven weeks after inoculation, all survivors—34 young and 26 old, as already noted—were killed and examined at autopsy.

All animals of each group were found to have generalized tuberculosis, although the amount of involvement of each of the several organs (spleen, liver, lungs, etc.) varied considerably. There was no apparent correla-

tion to be made out between size and age of animal and degree of pathological involvement. Several of the very largest (at time of inoculation) guinea pigs had the worst infection; some of the smallest had the least; but some small ones were quite bad while others were very good.

Comment on Result: The result was certainly not such as would support the idea that young animals in general, or, in this case, young guinea pigs, have less resistance to tuberculosis than that enjoyed by adults of the species. Variations of tuberculous involvement occurred, but they were variations that were not unlike for each set of guinea pigs; and, if one were to maintain that such variations were the end result of varying resistance, it was then plain that the several resistances were to be regarded as individual and in no respect attributes of a particular period of life.

TABLE 1

WEIGHTS OF YOUNG TUBERCULOUS ANIMALS			WEIGHTS OF YOUNG, NORMAL, NONTUBERCULOUS ANIMALS		
Cage III number	November 2 (30th day)	November 8 (36th day)	Cage II Number	November 2 (30th day)	November 8 (36th day)
	grams	*grams*		*grams*	*grams*
23	217	250	12	342	357
24	317	355	13	335	370
25	302	350	14	257	290
26	270	305	15	362	395
27	308	320	16	Died	
28	293	325	17	277	315
29	248	262	18	382	415
30	285	315	19	Died	
31	258	300	20	407	440
32	263	290	21	342	370
33	278	310	22	368	400

One might even contend that the evolution of the early local lesion and regional lymph-node changes, as well as the final results of the infection, pointed to a lesser resistance among the old animals, for the following reason:

The infecting dose was the same for all guinea pigs. The average weights at the time of infection were 596 gm. for the old and 237 gm. for the young animals. The former therefore weighed over twice as much as the latter, so that the young animals received, per body weight, over twice (in many individual instances much over twice) the numbers of bacilli applied to the old. The result showed that, whatever might be said about the sufficiency of the infection, the latter was heavy enough

to bring about generalized tuberculosis in the old guinea pigs and therefore, for much smaller animals, might be regarded as an overdose, so far as merely fulfilling the requirements for the production of generalized tuberculosis is concerned. The fact, then, that the young withstood the infection, as a general thing, as well as the old would suggest that they possessed a greater resistance. We mention this as a possible interpretation of the result, at the same time insisting that it does not seem justified because the number of animals is far too small and the conditions of the experiment not nearly restricted enough to control all the inherent variables that are familiar to every experienced experimenter in this field. The scope of the experiment would have to be greatly enlarged to settle this point definitely.

The final result, showing the young, as a class, no more seriously affected than the old, again makes necessary a revaluation, if possible, of the early changes due to the infection. That there were group differences here is unquestionable; they stood out as the prominent features of study, and all the more so because they were unexpected. Because, in response to the same infecting dose, local and regional lymph-node processes appeared earlier and went on to much greater development in the old, the phenomenon had the superficial earmarks of denoting a lower resistance for the old guinea pigs. But at the time, as has been related above in detail, we regarded such an inference as hasty and quite likely to be negatived by the ultimate outcome of the infection which, in the last analysis, must always be our measure of resistance in experiments of this nature. At the same time, there were observations which gave us definite and plausible reasons to view the occurrence in a different light; that is, that what we saw might quite easily by the result of local fixation of relatively many bacilli on the one hand (in the old) and relatively few on the other (in the young). Such a view presupposed, and indeed forecasted, that eventually more tuberculosis would be found to occur in the young. Since the latter event failed to appear our original hypothesis loses one of its strongest supports.

Our infecting dose was small though, as we have said, it was sufficient; and in work of this kind the ideal is always infections that, far from being overwhelming, are just large enough to bring about progressive infection uniformly. Only in this way can variables of resistance be best made out among animals all of which are susceptible to some degree. Nevertheless, the dose may have been too small. After intracutaneous inoculations fewer bacilli are, in general, carried from a depot of infection, and they are carried more slowly, than after subcutaneous infection. This

I have had abundant opportunity to observe in exhaustive and painstaking work that remains unpublished. I conceive it possible, therefore, though by no means even indicated by the present study, that our infecting dose was so small that not enough bacilli were moved rapidly enough from the portal of entry, even in those animals (the young) in which conditions most favored their transport, to produce internal tuberculosis tellingly enough. That is to say, the visceral infection evolved so backwardly in all cases that differences could be neutralized by other factors, such as those which, in another place (4), I have designated as the *accidents of time and place* in the metastasis of infection.

Again, as Roemer brought out long ago, it is now well known that when we approach minimal numbers of tubercle bacilli, in infecting guinea pigs, we arrive at quantities which will set up a generalized tuberculosis of very slow and very chronic course, one that may take months to terminate naturally even though bacilli are of high virulence. It is just as possible for differences of effect of infection to be obscured in excessively tardy and long-drawn-out tuberculosis as after overwhelming infection; and it is conceivable that this was the state of affairs in these "slight-infection" guinea pigs of our experiment.

At any rate the fact of the more vigorous response of the older animals, at the site of infection and nearby, to small numbers of tubercle bacilli, remains; and on the data at hand we are still inclined to regard this as the consequence of the fixation of more bacilli at or near the portal of entry in animals with naturally less open avenues of dissemination. The only other plausible explanation that appeals to us is the highly hypothetical one that the tissues of mature animals are by nature capable of reacting more quickly and more vigorously than those of immature animals of the same species to the same numbers of tubercle bacilli. If this were found to be a fact it would be one of the greatest fundamental importance, but whether the phenomenon could then be regarded as an expression of greater or less resistance would be altogether another matter and certainly one that could not be answered offhand.

EXPERIMENT 2

In this experiment the method of *inoculation* was subcutaneous in the groin, performed November 30, 1923. The experiment was terminated January 11, 1924, when all surviving animals were killed and examined at autopsy. The duration of the infection was therefore 42 days.

The *inoculated animals* comprised 49 young and 28 old guinea pigs. The average weight of the former was 235 gm. They ranged from 142 to 285

gm. The average weight of the old guinea pigs was 470 gm.; the range of weight was from 340 to 592 gm., although only three animals were below 400 gm. The average weight of the old was therefore exactly twice that of the young guinea pigs.

The *strain of tubercle bacillus used* was H37. The *inoculum* was 0.25 cc. of a suspension (physiological salt solution) that contained great numbers of tubercle bacilli. After a single, short centrifugation, to free it from the coarser clumps, the suspension remained heavy and turbid. *In this experiment, therefore, infection was performed with large or, as commonly designated, massive doses of tubercle bacilli.*

Course and Result of Experiment: In this experiment, with inoculation made subcutaneously, there was no opportunity to observe the first stages of anatomic reaction to the infection. The latter becomes evident only when enlargement and induration of the immediately adjacent lymph nodes make their appearance. These are always our earliest signs that infection has got under way. It is carried from the subcutaneous tissues of the groin, lymphatically, by channels that traverse the dorsum of the abdomen and thorax, to the junction of the jugular veins, and here entering the blood is then disposed to the body at large—first to the lungs and then to all other parts. As mentioned earlier, it can be shown, by using small enough numbers of bacilli, that subcutaneous infection is a more certain and more ready way to set up generalized tuberculosis than is intracutaneous infection. It assures the metastasis of more germs of a given *virulence* from the portal of entry to the interior of the body, and there is good reason to believe that a specified artificial infection is mobilized more rapidly after subcutaneous inoculation.

In this experiment there was again a marked difference of time of appearance of lymph-node involvement, as well as of the latter's extent, as between the two sets of animals. As early as the twelfth day after inoculation it was plain that involvement of the nodes was much more advanced in the old than in the young animals. It appeared earlier in the former and reached a much greater extent, and throughout the experiment the disparity continued striking. Our only explanation for this apparently greater tendency to local reaction in the old must again be that the more compact structure of the lymph nodes of mature guinea pigs makes for the interception of more bacilli on their way along the lymphatics, and that their greater involvement is thus the consequence of heavier topical infection.

The animals of this experiment were not weighed as frequently as those of the first experiment. Weighings of all animals were only biweekly for

the first month. We had used large infecting doses and had expected a rather rapid and severe tuberculosis. By the fourth week it was evident that this was in progress, for the constitutional signs of weak muscular tone were becoming marked. At the same time several of the animals were dying of a nontuberculous pneumonia and their autopsy disclosed foci of visceral tubercle.

The more "massive" infection had an undoubted effect on the animals' nutrition. While all young animals gained in weight, the increases were not nearly as marked as in the first experiment with its milder and more slowly developing infection. During the first month also there were, in general, slight gains among the old animals. After the first month had passed the only weighings made were of the members of selected cases on the day of ending the experiment. These disclosed a general tendency of both young and old animals to lose weight in the period between four and six weeks after infection.

During the experiment 14 young and 9 old animals died, or approximately the same proportion of each lot. Every one of the 9 old animals died of nontuberculous pneumonia which became mildly epidemic in the laboratory early in the winter. Of the 14 young guinea pigs, 10 died of the same pneumonia. The other four were free from pneumonia, and evidently died of tuberculosis which, while not extreme, was becoming extensive in them. All of these tuberculosis deaths occurred during the sixth week of the infection. Therefore, since pneumonia was prevalent and the young had begun to succumb to tuberculosis it was decided to terminate the experiment forthwith. This was done on January 11, 1924, exactly six weeks after inoculation.

All animals, young and old, were found to have generalized tuberculosis. In general, the old fared better than the young. However, an occasional old guinea pig had as much tubercle as the generality of the more involved young animals, while a very few young compared well with the old. As a rule, there was a greater dissemination of infection in the young. Few old animals had as much tubercle in their lungs as was noticeable in most of the young; nearly all of the latter had foci there, which, in most, were rather advanced. The livers of the old came off very much better than in the young, in which, as a rule, they were badly involved. The spleens averaged about the same for both lots.

Comment and Criticism on Result: The general result of experiment 2 was plain and definite: large doses of tubercle bacilli brought about more tuberculosis in young than in old guinea pigs. The meaning of this result, in terms of resistance, is not so explicit. If one regards the effects of

artificial tuberculous infection, such as are expressed by amount of involvement and the hastening of a fatal issue, as augmented by increasing numbers of bacilli introduced, and if one, in addition, considers that tubercle bacilli of specified virulence are invasive and devastating in proportion to their quantity per body weight of recipient, the conditions of the experiment allow another explanation of its results than that of a difference of resistance. The infection was, quantitatively, capable of causing fairly rapid and progressive disease of full-grown guinea pigs: there is hardly any doubt that if the experiment had been continued a few weeks longer these would have been dying of tuberculosis. In terms of body weight the infection was, quantitatively, twice as great for the young guinea pigs. And, in the absence of further information, one has as much right to attribute the result to an "overdosing" of the young animals as to lay it to their lower resistance.

When Kleinschmidt, in the study previously cited (3), infected his animals with quantities of bacilli proportioned to their body weight he could notice no difference, as between newly born and mature guinea pigs, in the resulting tuberculosis. This was, to be more precise, when his inoculations were 0.01 mgm. for 70 and 75 gm. guinea pigs, 0.03 mgm. for a 215 gm. animal, 0.07 mgm. for one of 520 gm. and 0.08 mgm. of 660 gm. When, however, he infected guinea pigs of different weights (from 40 to 670 gm.), all with the same dose (0.03 mgm.) of tubercle bacilli the older animals in most instances lived longer than the younger. Nevertheless, the number of listed animals is so very small and the exceptions are so glaring, that it is hard to see how any general valid conclusion can be drawn. For instance, one two-day-old guinea pig, of 40 gm., lived $2\frac{1}{2}$ months after receiving 0.03 mgm. tubercle bacilli, while after the same infection a 670-gm. animal died in two months. Estimating the nature of the resulting disease from the length of time of survival after infection and bringing together the results of all his inoculations, in so far as these relate to death within three months after infection, Kleinschmidt summarizes his results as follows: (1) In a series infected according to body weight 2 of 3 newly born and 6 of 9 adult animals died; and (2) in a series given equal infecting doses 6 of 6 newly born and 5 of 9 adults died. In view of the many variables concerned and the obvious necessity for exhaustive control observations, one may wish for much more extensive studies with more clean-cut results before accepting as established Kleinschmidt's broad generalization that "After infection according to weight newly born and adult animals behave similarly; on the other hand,

after the same infecting dose adult animals exhibit a much (*vielfach*) prolonged course of the disease."

Our own experiment, performed with equal quantities of bacilli, which we have considered as necessarily large merely to obtain generalized infection, arrived at results that are in accord with Kleinschmidt's general conclusion as to the effects of equivalent doses; that is, that young guinea pigs become more diseased than older animals. But our experiment with lighter infections, originated intracutaneously, does not support the generalization; for here with doses large enough to set up progressive disease in adults, but yet small enough to bring about a chronic rather than a fulminant condition, for two and a half months the young are, to all appearances, no more seriously affected than the old.

General Comment and Criticism: The experiments here reported, especially the second one, leave much to be desired. Their outcome suggests that if heavier infections had been used in the first experiment and lighter ones in the second, we may have come nearer to a satisfactory answer to the question of resistance at different ages. As it is, this answer is obscured by the possibility that what group variations of tuberculous involvement occurred were the result of variations of dosage in proportion to body weight of the animals.

Again, the second experiment would have been performed under better conditions if the differences in size and weight between young and old had been greater and sharper. We think that among the latter there were too many animals that were under 500 gm., and that it would have been better had there been a number of them over 600 gm. (the maximum weight at infection was 586 gm.). In this respect this element was much better arranged in the first experiment. As we see it now, we might also have controlled the second experiment better. We might, for instance, have given a number of the old animals twice the infecting dose. Such guinea pigs would then have been more comparable, as regards quantity of bacilli per body weight, with the young animals, and it is possible that the result of their infection might have indicated more definitely that the greater involvement in the young was an "overdosage" effect.

But, whatever technical defects may have attended this study, we do think that it did not bring to light a single feature to indicate that young guinea pigs are unusually susceptible to tuberculosis by reason of their immaturity. Indeed, when observed with our particular purpose in mind, they exhibited a resistance that was unexpectedly high. It was, after all, the matter of marked deficiency of resistance due to early age that we set out to investigate and we believe that the experiments answered this quite definitely in the negative.

The uniformly earlier anatomic reaction at the sites of infection and the subsequent more vigorous evolution of these foci in the mature animals impresses us as the most interesting disclosure of the experiments and as one that may be of the greatest fundamental importance. What appeared to be essentially a similar earlier and more intense reaction in the old animals of the experiment in which large doses of bacilli were introduced subcutaneously, that is, the more rapid and marked involvement of the regional lymph nodes in these animals, has probably the same bearing, whatever this may be. We are not prepared to explain the occurrence with finality, but at this time are inclined to view it as the result of a topical and neighboring lymphatic fixation of larger numbers of bacilli in older animals, and this greater fixation due in turn to the relative retardation of movement of bacilli in the more compact tissues that characterizes advancing age.

CONCLUSIONS

1. When young and old guinea pigs are infected intracutaneously with relatively small quantities of virulent tubercle bacilli that are equal for all the animals there is an earlier appearance and more vigorous development of tubercle at the site of inoculation and in the regional lymph nodes in the old animals.

2. After infection of this nature and heavy enough to cause generalized tuberculosis in the old animals, both young and old guinea pigs developed essentially the same grade of infection. There was nothing to indicate that the young were more susceptible than the old.

3. When infected subcutaneously with large quantities of virulent tubercle bacilli in equal dosage, a more extensive and progressive involvement resulted in the young than in the old.

4. Since under these circumstances the young received per body weight double the quantity of tubercle bacilli that was in itself sufficient to cause progressive and fatal tuberculosis in the old, it is likely that the more advanced infection of the young was the result of "overdosage."

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EDITORIAL

OSLER AND TRUDEAU

Musings on Cushing's Life of Osler

Osler was Anglo-Saxon with the charm of the Celt; Trudeau was half-French, half-American, with the charm of the French. Curiously, one came directly from Canada; the other claimed it as the land of his *voyageur* ancestor. Both were close to the pioneers of the New World; the father of one, the grandfather of the other lived on virgin soil. The one lived among, loved, and influenced great numbers of men. The other in youth was forced to seek opportunity in the wilderness, near the land of his forefather. Good health never failed the one and he died at seventy from a young man's disease. Ill health dogged relentlessly the steps of the other and his arch enemy claimed him after a struggle of over forty years at sixty-six.

Both were deeply interested in the problems of tuberculosis. Osler lived among the crowd and emphasized prevention. Trudeau dwelt in the wilderness with the individual, and spent day and night longing for the cure. Trudeau founded for the cure of the individual the first sanatorium in America. Osler was instrumental in bringing about the formation of the National Tuberculosis Association to carry the fight of prevention to the masses. Sociological prevention activated Osler; search for the Holy Grail of cure fascinated Trudeau. Trudeau thought in laboratory terms; Osler worked with laboratory exactness in clinical medicine. Both were deeply interested in but neither wrote on the early diagnosis of pulmonary tuberculosis. Trudeau searched for the early stage of the common proliferative type to arrest it; Osler was beguiled by the rare exudative form. Trudeau contributed much to scientific laboratory work in tuberculosis; Osler chiefly to the more general problems. Osler's work in tuberculosis influenced and stimulated many while he lived, including Trudeau. Trudeau's work to-day has become a tradition and still influences thousands.

The true estimate of the worth of any scientific worker, of his influence upon and good to the world, depends directly upon the number of workers to whom he passes on the torch of scientific investigation and in whom he instils the love of mankind. The work of Osler and Trudeau will be superseded, but the spirit they bequeathed to the following generation will eventually invade the uttermost parts of the earth.

L. B.

STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

I. THE RELATION OF EXPOSURE TO INFECTION IN 2000 CHILDREN EXAMINED FOR TUBERCULOSIS[2]

J. A. MYERS AND ESTELLA MAGIERA

How often one hears the statement that 90 to 95 per cent of all children become infected with tuberculosis by the time adult life is reached. This statement dates to the time soon after Pirquet announced the discovery of his test for tuberculous infection. Naturally enough, the test was applied first in Vienna, where it had been perfected. There Pirquet (1) and Hamburger and Monti (2) found high percentages of the children and young adults studied infected with tuberculosis. One must not overlook the fact that civilization is old in Europe and that tuberculosis is prevalent in the great cities. In these old and large cities there has been much crowding and intimate contact for years. Consequently, one would expect to find a high incidence of infection there. Even in Europe in the smaller cities, where tuberculosis is not so prevalent, one would expect to find a lower incidence of infection. Indeed, Barchetti (3) has pointed out that in Gratz, with a population of 150,000, where tuberculosis causes one-eighth of all the deaths, the incidence of infection among children from eleven to fourteen years of age is 58 per cent, while in Vienna, with a much larger population and where one-fifth of all the deaths recorded are due to tuberculosis, 94 per cent of the children between eleven and fourteen show evidence of tuberculous infection.

Spolverini (4) found, among 900 children less than one year old who were not suspected of having tuberculous infection, that 7 per cent reacted positively to the tuberculin test. Still (5) found, in a group of 658 children from the lower East Side of New York, that only 9.2 per cent reacted positively to the Pirquet test. These children ranged in

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age from two months to thirteen years. Although in no case was there a history of tuberculosis in the family, the parents were nearly all of foreign birth.

McLean and Jeidell (6), among 3742 medical cases seen at the Babies Hospital in New York, found 15.3 per cent reacting positively. Of 2000 in this group under one year of age 7.35 per cent gave positive reactions, whereas in 512 cases over three years old 32.24 per cent were positive. It is interesting to know that 75 per cent of a group of 433 proved tuberculous cases gave no history of exposure.

In connection with the Framingham demonstration, Armstrong (7) reported 460 tests on children between the ages of one and seven years. Between ages six and seven, 33 per cent of the children reacted positively to the skin test. It is interesting to note that a higher incidence of infection was reported among the female children, 55 per cent of whom gave positive reactions, while only 38 per cent of the male children were positive. In the second year it was found that 15 per cent of the children reacted to the tuberculin test. The incidence increased from this time until the seventh year, when 54 per cent were positive.

Dunn and Cohen (8) found that 20 per cent of autopsies on 661 children under two years old revealed definite tuberculous lesions. Their studies led them to believe that a negative Pirquet reaction in children under two years is not sufficient evidence to rule out tuberculosis, but that a positive test is diagnostic of tuberculosis at this age.

In the province of Saskatchewan, Canada, Ferguson (9) found that 56.6 per cent of 1346 children ranging in age from six to fourteen years showed evidence of tuberculous infection.

Fürstner-Risselada (10) called attention to the fact that in The Hague (Holland) the percentage of infected children is much lower than that reported by Hamburger and Monti of Vienna. Of 1506 children examined, positive reactions were found in 20 per cent of the children of six and seven years. Above this age there was a gradual increase in positive reactions, until the last age studied (thirteen years), when the incidence reached 50 per cent.

Peiser (11) has pointed out that in German cities the incidence of tuberculous infection among the school children averages from approximately 56 per cent among the younger ages to approximately 66 per cent among the older ages.

Brüning (12) had Pirquet tests performed on 350 children from the better classes. The cases were not selected in any way. Of the entire

number, ranging from infancy to fourteen years of age, 26 per cent showed positive reactions.

Hoffa (13) states that Czerny and Moro have shown that universal infection by tubercle bacilli is a myth. Observations on 7000 children showed that only 40 to 60 per cent of those in the tenth to fourteenth years reacted positively to tuberculin.

Arnfinsen (14) found that 37.8 per cent of 6978 public school children in Tronhjem were infected, while of 991 private school childen in the same city 33 per cent were infected.

Sander (15) studied 992 children in Dortmund. In 869 of these, infection had occurred in 6 per cent at two years of age and in 50 per cent at thirteen to fourteen years. The remaining 123 of the total number studied had manifest tuberculosis. It is believed that the small percentage of tuberculous people in Dortmund accounts for the low incidence of tuberculous infection in children.

After studying the frequency of tuberculous infection in 1321 children in St. Louis, Veeder and Johnson (16) state:

> The extent of infection among children varies in different cities and countries and is dependent on such factors as living and social conditions, the amount of tuberculosis in the community, the exposure of the child to open tuberculosis, and in all probability varies among different classes of society in the same community. No conclusions as to the extent of infection with the tubercle bacillus can be drawn from the statistics of any one city or class, and the statement that "90 per cent or more" of individuals are infected by puberty is an extreme exaggeration of the actual conditions which exist.

Slater's (17) recent work aroused considerable interest in the subject of tuberculous infection in childhood. He pointed out that in a rural community in Minnesota the incidence of infection is extremely low. Although he made tests on 1654 children he believes the low incidence of infection is due to the fact that his study was made in a wealthy farming community where a very low tuberculosis death-rate prevails, where living conditions are good, and where the people are intelligent and coöperative in combating tuberculosis. Of the total group studied Slater found approximately 10 per cent reacting positively to the tuberculin test. He also found from this study of 1654 school children that in 563 cases with no history of exposure only 5 per cent reacted positively to the Pirquet test; in 1025 cases with histories of doubtful exposure 8 per cent reacted positively; but in 67 cases with known history of ex-

posure 80 per cent reacted positively. Slater concludes that "It is practically impossible for a child to remain in the home with an open case of tuberculosis and not become infected." After making a study of the spread of tuberculosis in families Lampson (18) concluded:

First, that the spread of tuberculous infection in families where open cases of tuberculosis exist is greater than it is generally understood to be. Sixty-seven per cent of the individuals of these families, excluding the centre cases, show evidence of tuberculous infection. In no case where there has been definite, proved exposure of a family to an open case of tuberculosis, no matter what precautions have been taken, have I failed to find a spread of infection. In at least ten cases investigated the infection has spread to the limit of available material. Every member of these ten families shows evidence of tuberculous infection.

Second, that in families where no cases of tuberculosis have been found, no matter what the home life or living conditions were, the number of individuals showing evidence of tuberculous infection was small, namely 2.5 per cent.

Third, that in families where cases of latent tuberculosis exist, the spread of infection is not as great as in families where open cases of tuberculosis are found, 22 per cent against 67 per cent.

Fourth, that in families where healed cases of tuberculosis are present, the spread of infection is less than in families where open cases exist, 33 per cent against 67 per cent.

Fifth, that in families where no tuberculosis is found, the number of individuals showing evidence of infection is very small (2.5 per cent) in comparison with the families in which open, latent, or healed tuberculosis exists.

Röpke (19) found that 67.5 per cent of a group of nurslings associated with tuberculous patients were infected, while 84 per cent of a group of children of two years with similar associations were infected with tuberculosis.

Wahl and Gerstenberger (20), studying children from six weeks to four years of age, found positive tuberculin reactions in 44 per cent of those giving positive histories of exposure, while only 15 per cent of those giving negative histories were infected.

Barchetti (21) made a study of 51 infants of mothers who had definitely active tuberculosis. These infants were observed over periods varying from several months to one year, and examinations were made subsequently up to the second and fourth years. Of the entire group studied 27 per cent remained uninfected, although a part of these were breast-fed. The remaining 73 per cent became infected. Seventy-one per cent of those infected died of tuberculosis.

Reuben (22) has called attention to 42 cases reported in the literature of infants becoming infected from ritual circumcision. These are usually traced to operators who suffered from tuberculosis.

Bernard and Debré (23), observing 123 infants associated with tuberculous mothers, found that all of those in contact with the mothers over six months contracted the disease. It is of great interest and practical significance to know that some infants do not become infected for a considerable time. In some cases infants were saved from infection after association with the mother of periods varying from eight days to three months. On the other hand it is discouraging to know that a high percentage of the infants that did become infected died within a month after removal from their mothers. The mothers of 58 of the children of the entire group had tubercle bacilli in the sputum, while in the remaining 65 mothers tubercle bacilli were not demonstrated. Only 18 of the infants lived whose mothers showed bacilli, while 57 lived whose mothers did not show bacilli in the sputum.

Schloss (24) calls attention to the case of a nurse found to have advanced tuberculosis while on a pediatrics service. The investigation for tuberculosis carriers was prompted when it was learned that a very high percentage of the infants on that service were infected with tuberculosis. When the carrier was found to be a nurse it was shown that all the infants in her ward were infected except two who were breast-fed by their mothers. In another ward where this nurse had substituted only temporarily it was found that 33 per cent of the infants were infected.

One might continue citing the results of many more investigations in various parts of the world, but those already mentioned reveal the fact that there are wide variations in the incidence of tuberculous infection in various parts of the world. Hamburger (25) believes these variations may be explained in the following three ways: first, by actual variation in the incidence of the disease; second, by difference in the methods used for examination; and third, by difference in the selection of the material.

Our data were taken from records of the out-patient department of the Lymanhurst School for Tuberculous Children. In this department any child from birth through school age may be examined. Some children were brought for examination because their families believed in periodic examinations, but most of them were brought because of exposure to tuberculosis or some symptom which had suggested tuber-

culosis to school physicians, school nurses, teachers, parents, or others interested in their health.

In going over our records it was found that with regard to exposure our cases fell into three groups as follows: *Group I*, consisting of those with definite history of exposure; *Group II*, consisting of those in whom history of exposure was questionable or history unsatisfactory; and *Group III*, consisting of those whose records showed no history of exposure.

In all, 2000 children were examined (fig. 1). Of this number 1033 were girls and 967 were boys. They ranged in age from a few months to nineteen years. Of the girls examined 440 were positive to the Pirquet test while 393 boys gave positive reactions. It is obvious that our data do not agree with those of Cornet (26) and others, who have found a higher incidence of tuberculosis among girls than among boys. The percentages of the boys and girls combined reacting positively and negatively to the Pirquet test at different ages are represented graphically in figure 2. It will be seen that the incidence of infection increases somewhat with age but not as regularly and to the same extent as many authors have found. In this connection Slater (17) concluded that "The percentage of those reacting to the Pirquet test in a rural community does not increase as one advances in age to the extent generally taught."

In grouping our cases according to exposure we found 761 giving histories of intimate contact with definitely tuberculous patients, another group of 784 with no knowledge of ever having come in contact with a tuberculous patient, and a third group of 455 whose histories were questionable, that is, not enough evidence could be gathered to warrant a definite statement. These cases are shown according to age in table 1 and in figure 3.

Table 1 and figure 4 show that the Pirquet tests were positive in 435 of the 761 cases with definite histories of exposure, in 224 of the 784 with no histories, and in 174 of the 455 cases with questionable histories of exposure. Figure 5 shows the percentage of cases in the three exposure groups with negative Pirquet reactions. The time which had elapsed since the beginning of the period of exposure and the examination was not considered. Marfan (27) has pointed out that in most cases from twenty to thirty days elapse from the time tubercle bacilli are ingested until the skin test becomes positive. However, he gives the extremes as six days and four months. Of course, it is often difficult to determine just when tubercle bacilli were first ingested.

TABLE 1

RELATION OF HISTORY OF EXPOSURE TO REACTION TO VON PIRQUET TEST
BOYS & GIRLS; 2000 CASES

Age in Years	Total Number of Cases	Cases with Positive Von Pirquet Reaction		History of Exposure in Positive Von Pirquet Cases			Cases with Negative Von Pirquet Reaction		History of Exposure in Negative Von Pirquet Cases		
		Number	Percentage	Definite	Questionable	None	Number	Percentage	Definite	Questionable	None
Less than 1 year	39	16	41.0	10	6	0	23	59.0	13	8	2
1	32	12	37.5	8	3	1	20	62.5	9	8	3
2	65	24	36.9	16	4	2	41	63.1	27	11	3
3	71	24	33.8	17	4	3	47	66.2	16	16	15
4	97	37	38.2	26	7	4	60	61.8	33	16	11
5	102	41	40.2	24	9	8	61	59.8	27	16	18
6	170	60	35.3	36	11	11	110	64.7	32	31	47
7	175	67	38.3	33	15	19	108	61.7	27	14	67
8	196	81	41.3	39	21	21	115	58.7	29	30	56
9	176	84	47.7	44	13	27	92	52.2	15	14	63
10	177	86	48.6	35	19	32	91	51.4	14	24	53
11	181	77	42.5	33	13	31	104	57.5	24	23	57
12	142	64	45.1	34	9	21	78	54.9	17	21	40
13	184	60	48.4	26	15	19	64	51.6	9	20	35
14	118	49	41.5	28	10	11	69	58.5	15	13	41
15	87	34	39.1	14	9	11	53	60.9	13	11	29
16	26	11	42.3	6	3	2	15	57.7	2	3	10
17	11	3	27.3	1	2	0	8	72.7	0	1	7
18	9	2	22.2	0	1	1	7	77.8	2	1	4
19	2	1	50.0	1	0	0	1	50.0	0	0	1
Total:	2000	833	41.7	435	174	224	1167	58.3	326	261	580

TABLE 2

RELATION OF HISTORY OF EXPOSURE TO REACTION TO VON PIRQUET TEST
GIRLS; 1033 CASES

Age in Years	Total Number of Cases	Cases with Positive Von Pirquet Reaction		History of Exposure in Positive Von Pirquet Cases			Cases with Negative Von Pirquet Reaction		History of Exposure in Negative Von Pirquet Cases		
		Number	Percentage	Definite	Questionable	None	Number	Percentage	Definite	Questionable	None
Less than 1 year	17	7	41.2	5	2	0	10	58.8	3	6	1
1	13	3	23.1	3	0	0	10	76.9	4	5	1
2	26	12	46.1	8	2	2	14	53.8	9	5	0
3	37	13	35.2	10	2	1	24	64.8	11	8	5
4	50	15	30.0	10	4	1	35	70.0	19	8	8
5	33	21	38.6	14	4	3	32	60.4	15	10	7
6	96	36	37.5	22	6	8	60	62.5	19	16	25
7	88	32	36.4	18	4	10	56	63.6	12	5	39
8	94	37	39.3	17	9	11	57	60.6	11	18	28
9	77	37	48.1	16	5	14	40	51.9	5	8	27
10	94	33	36.4	22	10	21	41	43.6	7	8	26
11	102	42	41.2	19	6	17	60	58.8	14	13	33
12	80	41	51.2	22	9	10	39	48.8	6	14	19
13	75	32	42.7	15	5	12	43	57.3	5	13	25
14	62	29	46.8	15	7	7	33	53.2	7	7	19
15	46	22	47.8	7	6	9	24	52.2	7	1	16
16	9	3	33.3	2	1	0	6	66.7	0	2	4
17	6	2	33.3	1	1	0	4	66.7	0	1	3
18	6	2	33.3	0	1	1	4	66.7	0	1	3
19	2	1	50.0	1	0	0	1	50.0	0	0	1
Total:	1033	440	42.6	229	84	127	593	57.4	154	149	290

TABLE 3

RELATION OF HISTORY OF EXPOSURE TO REACTION TO VON PIRQUET TEST
BOYS; 967 CASES

Age in Years	Total Number of Cases	Cases with Positive Von Pirquet Reaction		History of Exposure in Positive Von Pirquet Cases			Cases with Negative Von Pirquet Reaction		History of Exposure in Negative Von Pirquet Cases		
		Number	Percentage	Definite	Questionable	None	Number	Percentage	Definite	Questionable	None
Less than 1 year	22	9	40.9	5	4	0	13	59.1	10	2	1
1	19	9	47.3	5	3	1	10	52.7	5	3	2
2	39	12	30.7	10	2	0	27	69.3	16	6	5
3	34	11	32.3	7	2	2	23	67.7	7	8	8
4	47	22	46.8	16	3	3	25	53.2	14	8	3
5	49	20	40.8	10	5	5	29	59.2	12	6	11
6	74	24	32.4	16	5	3	50	67.6	13	15	22
7	87	35	40.2	15	11	9	52	59.8	15	9	28
8	102	44	43.1	22	12	10	58	56.9	18	12	28
9	99	47	47.4	26	8	13	52	52.5	10	6	36
10	83	33	39.8	13	9	11	50	60.2	7	16	27
11	79	35	44.2	14	7	14	44	55.7	10	10	24
12	62	23	37.0	12	0	11	39	62.9	11	7	21
13	49	28	57.1	11	10	7	21	42.9	4	7	10
14	36	20	55.7	13	3	4	36	64.3	8	6	22
15	41	12	29.2	7	3	2	29	70.7	6	10	13
16	17	8	47.0	4	2	2	9	52.9	2	1	6
17	3	1	20.0	0	1	0	4	80.0	0	0	4
18	3	0	0.0	0	0	0	3	100.0	2	0	1
19	0	0	0.0	0	0	0	0	0.0	0	0	0
Total:	967	393	40.6	206	90	97	574	59.4	172	132	270

TABLE 4

PERCENTAGE RELATION OF HISTORY OF EXPOSURE
TO REACTION TO VON PIRQUET TEST
BOYS & GIRLS; 1978 CASES

Age in Years	Definite Exposure			Questionable Exposure			No History of Exposure			Total	
	Percent of total	Positive Von Pirquet	Negative Von Pirquet	Number and Percent of total	Positive Von Pirquet	Negative Von Pirquet	Percent of total	Positive Von Pirquet	Negative Von Pirquet	Positive Von Pirquet	Negative Von Pirquet
Less than 1 year	30.9	40.9	59.1	33.9	46.7	53.3	5.2	0.0	100.0	41.0	59.0
1	33.1	47.1	52.9	34.4	27.3	72.7	12.5	25.0	75.0	37.5	62.5
2	69.2	60.0	40.0	23.1	26.7	73.3	7.6	40.0	60.0	36.9	63.1
3	49.3	47.2	52.8	28.2	21.1	78.9	22.5	17.6	82.4	33.8	66.2
4	60.8	43.1	56.9	23.7	33.3	66.7	15.5	36.6	63.4	38.2	61.8
5	50.0	46.9	53.1	24.7	40.0	60.0	25.3	28.6	71.4	40.2	59.8
6	41.2	54.3	45.7	24.7	27.3	72.7	34.1	19.5	80.7	35.3	64.7
7	34.3	55.9	44.1	18.9	50.0	50.0	46.8	22.4	77.6	38.3	61.7
8	34.7	51.6	48.4	28.0	44.4	55.6	39.3	26.3	73.7	41.3	58.7
9	33.3	74.6	25.4	15.3	51.7	48.3	51.2	29.2	70.8	47.7	52.3
10	27.6	70.2	29.8	24.2	48.9	51.1	48.2	36.1	63.9	48.6	51.4
11	31.4	58.2	41.8	19.3	39.5	60.5	49.3	33.3	66.7	42.5	57.5
12	33.9	66.7	33.3	21.1	30.0	70.0	45.0	34.4	65.6	45.1	54.9
13	28.2	74.3	25.7	28.2	40.0	60.0	43.6	35.0	64.2	48.4	51.6
14	36.4	67.4	32.6	19.4	43.5	56.5	44.2	21.2	78.8	41.5	58.5
15	31.0	51.9	48.1	22.9	45.0	55.0	46.1	28.8	71.2	39.1	60.9
16	30.7	73.0	25.0	25.0	50.0	50.0	46.3	16.7	83.3	42.3	57.7

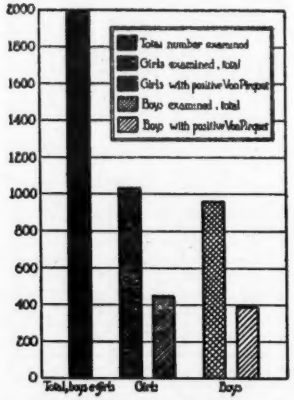

FIG. 1. RESULTS OF VON PIRQUET TEST
(967 BOYS, 1033 GIRLS)

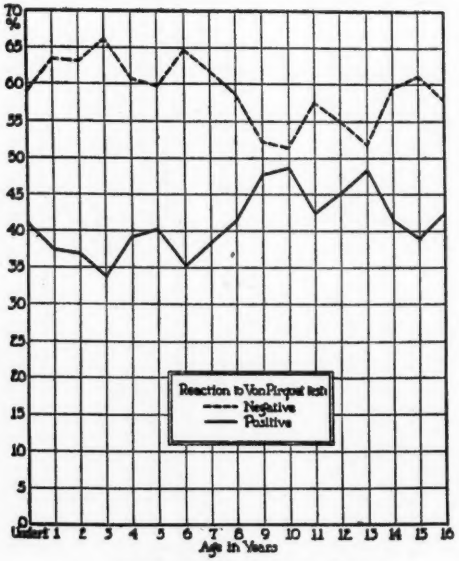

FIG. 2. RESULTS OF VON PIRQUET TEST
(2000 BOYS AND GIRLS)

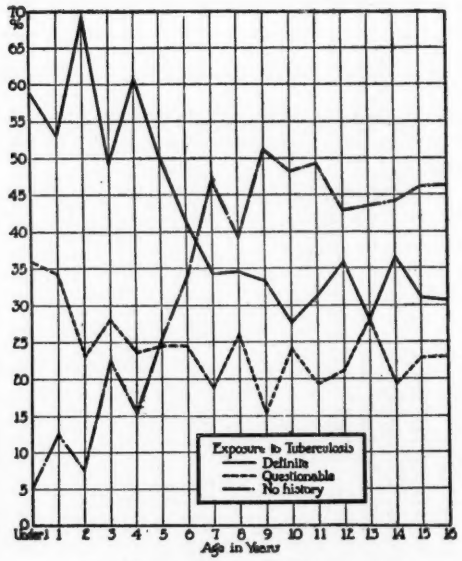

FIG. 3. DATA OF EXPOSURE TO TUBERCULOSIS
(2000 BOYS AND GIRLS)

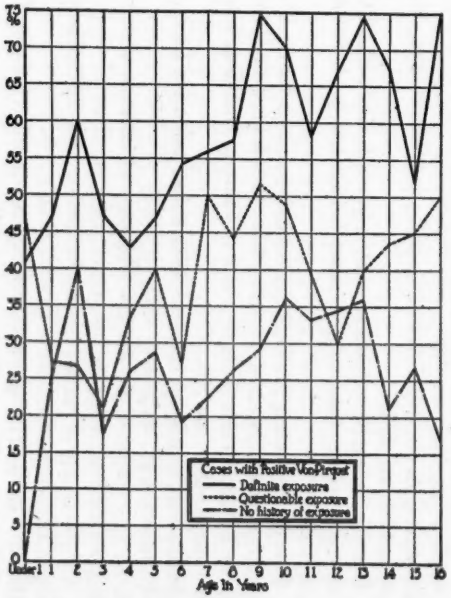

FIG. 4. RELATION OF HISTORY OF EXPOSURE TO TUBERCULOSIS TO POSITIVE VON PIRQUET REACTION (2,000 BOYS AND GIRLS)

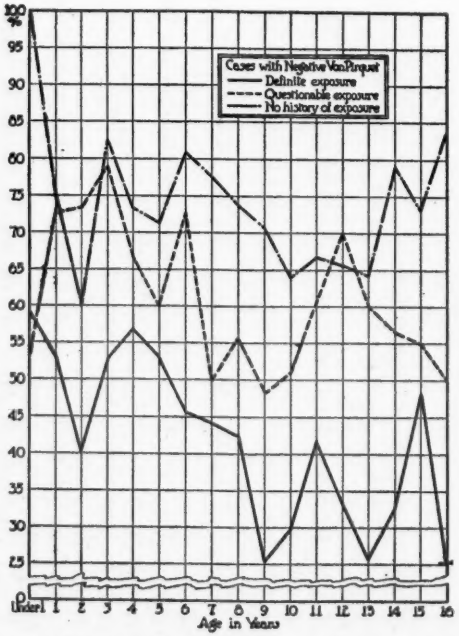

FIG. 5. RELATION OF HISTORY OF EXPOSURE TO TUBERCULOSIS TO NEGATIVE VON PIRQUET REACTION (2,000 BOYS AND GIRLS)

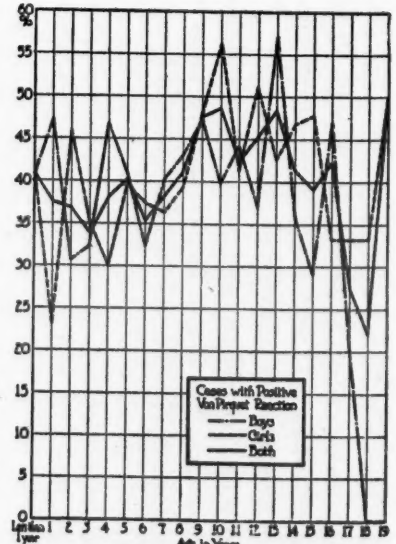

FIG. 6. EIGHT HUNDRED AND THIRTY-THREE CASES WITH POSITIVE VON PIRQUET REACTION (393 BOYS, 440 GIRLS)

When the girls were considered separately (fig. 6 and tables 2 and 4) the Pirquet tests were positive in 229 of the 383 with definite histories of exposure, in 127 of the 417 without histories of exposure, and in 84 of the 233 with questionable histories of exposure.

When the boys were considered separately (fig. 6 and tables 3 and 4) the Pirquet tests were positive in 206 of the 378 cases with definite histories of exposure, in 97 of the 367 without histories of exposure and in 90 of the 222 with questionable histories of exposure. It is obvious, therefore, that the incidence of tuberculous infection is definitely higher among those children with histories of exposure than among the other two groups.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

II. THE DETECTION OF THE PRIMARY LESION IN A GROUP OF CHILDREN EXAMINED FOR TUBERCULOSIS[2]

J. A. MYERS AND E. O. LODMELL

It is a well-known fact that the incidence of tuberculous infection in children varies considerably in different parts of the world. Just where the primary tuberculous lesion usually occurs has been a subject of considerable controversy. It has been pointed out by Cummings (1) that in tuberculosis there are two main orders of pathological phenomena; namely, those of primary localization and those of secondary localization. With the lesions of primary localization he includes the point of entry, the neighboring lymph nodes and the intervening lymphoid tissue and lymphatic vessels. The lesions of secondary localization are due to bacilli which escape from the area of primary localization. There bacilli may travel along the ramifications of the bronchi or along the digestive tract but Cummings believes the blood-stream is their most common carrier.

The area of primary localization may be in any one of many parts of the body, such as the skin, the ear, the tonsils, the intestine and the lungs. The external auditory meatus has been reported to be the site of the primary lesion as a result of digital infection. Krause (2) has called attention to the fact that observers have detected tuberculosis of the tonsils and adenoids in about 5 per cent of large series of cases. Moreover, infection of the cervical lymph nodes is the most frequent manifestation of clinical tuberculosis between the ages of three and ten years. He believes, therefore, that this high incidence of nasopharyngeal and cervical infection in children should establish a common locus of early infection. That the area of primary localization may involve the intestine and mesenteric lymph nodes is a well-established fact; however,

[1] From the Lymanhurst School for Tuberculous Children, Minneapolis, and the Departments of Internal Medicine and Preventive Medicine, University of Minnesota.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

it is believed that this is not the most common site of this area. Indeed, Rijssel (3) after examining at postmortem the bodies of 776 children, 187 of which were tuberculous, concluded that primary intestinal tuberculosis is rarely found anatomically. Carson (4) found that the mesenteric lymph nodes may be the only part of the body involved with tuberculosis. In discussing primary tuberculosis of the mesenteric nodes, Gehrels (5) states that it is produced by bacilli entering from the intestine and that it is more common in children than adults. He states further that the bovine type of bacillus is common in such cases.

Beitzke (6) found primary lesions in the intestine in 4.4 per cent of 1100 cases postmortem. Wollstein and Spence (7) on a large number of autopsies found tuberculosis primary in the digestive tract in only 9 cases.

Opie (8) says

> The foregoing study of tuberculosis in adults who, with one exception, have died with conditions wholly unrelated to tuberculosis has shown that evidence of first infection with tuberculosis may be found in the mesenteric lymph nodes of one of every four young British adults, whereas similar lesions are relatively uncommon in this country. The greater frequency of tuberculosis among cattle in Great Britain suggests itself as an explanation. It is noteworthy that in those in whom these mesenteric lesions occur focal tuberculosis of the lung is scant or absent.

From our present knowledge it appears that usually the lungs and adjacent lymph nodes are most commonly involved primarily. Gohn (9) from autopsy studies on 184 cases concluded that there is usually only one primary infection and that this lies in the lung subjacent to the pleura. This primary focus he states is always accompanied by involvement of a lymph node draining the primary focus. More recently Gohn and Winternitz (10), after studying at autopsy 608 bodies, conclude that more than 97 per cent of primary lesions occur in the lungs.

From a recent study Opie (11) concluded that:

> Active pulmonary tuberculosis (phthisis) is always accompanied by evidence of a preceding tuberculous infection. Calcified foci of healed tuberculosis are present in the lung substance and in adjacent lymph nodes. These calcified lesions found in the lungs of those who die with phthisis are usually less extensive than those found in the lungs of adults who have died from other causes.

Such primary lesions have also been reported by Ranke (12), Zimmermann (13), Fischl (14), Canti (15), Konyevitis (16), Müller and

Klinckmann (17), Lange (18), Wollstein and Spence (7), and others. These workers believe the bacilli are carried to the lungs by the inhaled air.

On the other hand, Calmette (19) is strongly of the opinion that in the great majority of cases the infection takes place by way of the digestive tract, the bacilli gaining entrance to the body through the buccal, pharyngeal and intestinal mucous membranes. From these mucous membranes he believes the bacilli are usually taken up by blood elements and carried to the places of primary localization, usually leaving no trace of their existence on the mucous membranes through which they passed. Calmette believes that the primary lesion develops in the bronchial lymph nodes much more often than in the lung parenchyma. Calmette and Grysez (20) have shown that when tubercle bacilli are placed upon the mucous membranes of the eye of animals there appears first an enlargement of the cervical lymph nodes, later an enlargement of the tracheobronchial lymph nodes, and after this an involvement of the lung parenchyma appears.

The material for our report consists of the children examined in the out-patient department of the Lymanhurst School for Tuberculous Children. When this department was established it was believed that stereoscopic X-ray plates should be taken only occasionally when some indication exists. As time passed, however, we were convinced that not infrequently enlargement of the hilum nodes, primary foci and other slight parenchymal lesions were escaping detection. Since that time stereoscopic plates have become a routine procedure in the examination of children in the Lymanhurst out-patient department.

In this report we have included 1412 patients, all of whom have had stereoscopic X-ray plates, histories, physical examinations, etc. Of these 1412 cases, 232 showed shadows in the lungs which the roentgenologists interpreted as primary foci of tuberculosis. Obviously, the X-ray interpretation is not infallible, as other conditions may result in shadows which closely simulate those due to primary tuberculous foci. The autopsy finding is the only evidence, therefore, upon which one may rely with absolute safety.

Aschoff (21) has recently called attention to the findings of pathologists to the effect that typical bone develops around primary tuberculous foci in the lungs. This he further points out serves as a point of differentiation between primary foci and those produced through reinfection. When true bone has formed one would expect a sharply out-

lined shadow to appear on the X-ray plates and that this shadow would be present in serial plates taken over long periods of time. Occasionally, one sees a case in whom the roentgenologist on first examination reports a primary focus in the lung, while several months later from new plates he is unable to confirm his former finding. One could hardly believe that with a standard technique of exposure and development of plates there could be enough difference in the second plates to make it impossible to visualize the shadow formerly seen. It seems more probable that the shadow originally seen was due to some other process. Again, one must not overlook the possibility of a primary focus healing so as to leave no demonstrable evidence of its existence. Enough work has been done by pathologists to convince us that X-ray shadows interpreted as representing primary foci are often confirmed at autopsy. In this connection it is hoped that it will be found possible to make serial X-ray plates over long periods of time of many Lymanhurst children.

Among our 232 children showing evidence of primary foci by the X-ray, 152 gave definite histories of exposure (fig. 1). The remainder gave questionable or no histories of exposure. There were among these 232 children 145 who reacted positively to the Pirquet test.

The location of the primary lesion in the various lobes of the lungs is of considerable interest. The following table shows their distribution from the autopsy studies of Gohn, Opie, and Wollstein and Spence:

	GOHN	OPIE	WOLLSTEIN AND SPENCE
Right upper lobe	51	7	17
Left upper lobe	50	5	16
Left lower lobe	40	5	16
Right lower lobe	39	5	13
Right middle lobe	14	5	11

In our group of cases the X-ray shadows interpreted as primary foci were most commonly found in the lower lobes, particularly the right lower lobe (fig. 2). A much smaller number were found in the upper lobes, and the smallest number in the right middle lobe.

Since approximately 45 per cent of our 1412 cases reacted positively to the Pirquet test and only 232 presented X-ray evidence of primary foci in the lung parenchyma, it would appear that many primary foci develop elsewhere. In a good number of our cases with positive Pirquet reactions and no X-ray evidence of primary foci in the lungs, there was

definite X-ray evidence of hilum node enlargement. To be sure, there are many causes of hilum node enlargement other than tuberculosis. Nevertheless, Wollstein and Spence in their group of children studied at autopsy found primary lesions in the bronchial lymph nodes fifty-seven times.

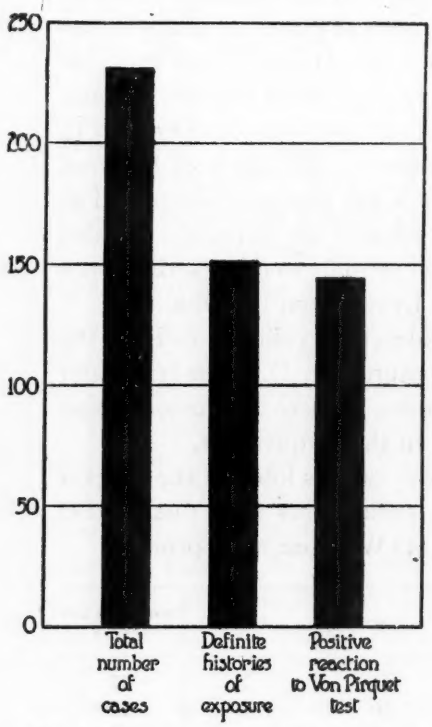

FIG. 1. CASES SHOWING STEREOSCOPIC X-RAY EVIDENCE OF PRIMARY FOCI

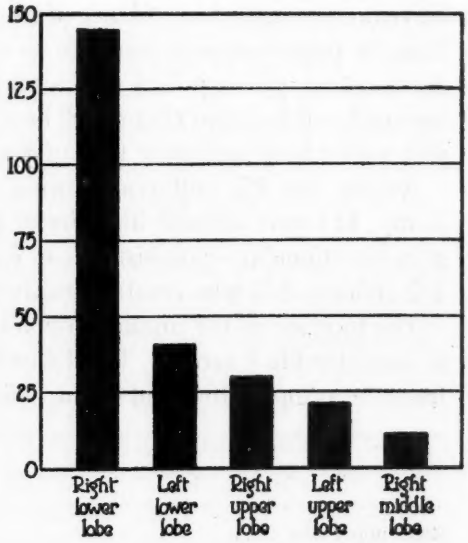

FIG. 2. CASES SHOWING STEREOSCOPIC X-RAY EVIDENCE OF PRIMARY FOCI IN VARIOUS LOBES OF THE LUNG

In discussing the lesions of first infection with tuberculosis Opie and Andersen (22) say

Study of these lesions of first infection with tuberculosis has been much neglected, but is essential to an understanding of the mode of tuberculous infection and the conditions under which it occurs. The size and extent of the lesions which have been described demonstrate that they are not without clinical significance and have probably been accompanied by symptoms such as pyrexia and diminution of body weight.

With few exceptions an X-ray plate made from the lung of an adult demon-

strates the presence of conspicuous calcified nodules in the lung and in adjacent lymph nodes, whereas in approximately half of all adults the healed pulmonary nodules, which are usually multiple, are from 0.5 to 1 cm. in diameter, and the more numerous nodules of the lymph nodes are from 1 to 2 cm. across (group 2). It is probable that these lesions were considerably larger and more numerous in their active stage, for tuberculous lesions tend to resolve when recovery occurs and persist as calcified masses only when caseation has been present. In more than one in every ten individuals the calcified lesions present in the lung at autopsy show that the individual has suffered with widely disseminated tuberculosis of the lung and massive tuberculosis of the adjacent lymph nodes (groups 3 and 4). Evidence of extension of the tuberculous infection to distant organs is not uncommon and healed tubercles in the liver or spleen, usually in both, have been found in 10 of 14 instances of extensive healed tuberculosis of the lungs.

In treating this subject one must ever be cognizant of the fact that X-ray findings whether positive or negative, although of great value, are not infallible.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

III. THE INCIDENCE OF CHRONIC PULMONARY LESIONS IN A GROUP OF CHILDREN EXAMINED FOR TUBERCULOSIS[2]

C. O. ROLLIE AND J. A. MYERS

In all tuberculosis work there exists no more interesting study than that of the method of attack of the tubercle bacillus on the human body at different ages of life. It is generally believed that prenatal infection occurs only rarely. It is generally believed, too, that after birth the child is very susceptible to tuberculous infection and when infection occurs it results in a high percentage of fatalities during the first two or three years of life, this being especially true during the first year. During this early period the disease may attack any one of a number of organs primarily but there is a strong tendency for it to become generalized. In other words, the body offers little resistance in many cases.

It is now believed that when the lung is involved before the age of three or four years one of two things usually occurs: first, there may be fairly rapid healing of the lesions resulting in the healed primary focus, evidence of which is found in later life by the roentgenologist and the pathologist; and second, there is a rapid spread of the disease soon resulting in death. A third, but much less common occurrence, is the development of chronic pulmonary tuberculosis.

The group of cases we are reporting were examined in the out-patient department of the Lymanhurst School for Tuberculous Children. Here one would expect a good-sized number of children with healed primary foci. In fact, this group of cases has been considered in another paper (1). In an out-patient department for children one would expect to see few or no cases acutely ill with the rapidly developing type of pulmonary tuberculosis of childhood. Such cases are usually seen in private practice in the homes and in hospital practice. Many such cases are

[1] From the Lymanhurst School for Tuberculous Children, Minneapolis, and the Departments of Internal Medicine and Preventive Medicine, University of Minnesota.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

reported in the literature. Indeed, Siperstein and Bauguess (2) recently reported the case of a two-year-old boy who died of tuberculosis. The autopsy report showed pulmonary tuberculosis with cavities in the right lung, miliary tuberculosis of the spleen and liver, slight bronchopneumonia, fibrinous and fibrous pleurisy and tuberculous adenitis. These authors discuss at some length the occurrence of pulmonary cavities in the lungs of infants suffering from tuberculosis and point out that the occurrence of cavitation "while indeed uncommon is not at all rare." A number of other authors including Ausset (3), Babeau (4), Comby (5), Delarde (6), Geipel (7), Kuss (8), L'Homme (9), Leroux (10), Mairesse (11), Randolph (12), Schott (13), and White (14) have reported extensive acute involvement including cavitation in the lungs of infants.

It is the much less common occurrence, namely, the development of chronic pulmonary tuberculosis in childhood to which we wish to give especial consideration in this paper.

Because of the differences between the normal chest of the child and the adult the diagnosis of chronic lesions in the lungs of children was in time past attended with considerable difficulty. With the advent and subsequent development and use of the X-ray, however, such lesions, although not common, are more frequently detected. Moreover, careful autopsy studies of children have thrown much light upon this subject. In speaking of apical tuberculosis Opie (15) states that it "begins in adult life or occasionally in the later period of childhood and pursues a chronic course characterized anatomically by abundant formation of fibrous tissue."

Krause (16) reported a case of multiple tuberculosis in childhood in which he found infiltration of the right lung. The pulmonary infection was of a very slow and benign character. Although this child was fourteen years of age his first lesion was manifested when he was only four years old by an abscess in the left ulnar region which followed an injury to his arm. Following this lesion tibial, inguinal, epitrochlear, axillary and costal tuberculosis developed. Then appeared mesenteric, cervical and bronchial lymph-node, and pulmonary involvement. Under the proper treatment this case responded nicely. Krause points out that this case illustrates the favorable prognosis of tuberculosis in childhood.

Bartlett and Wollstein (17) state that, "The real difference between tuberculosis in infancy and in later life lies in the fact that practically all lesions seen at autopsy in children under two years of age are acute. Fibrosis is unknown and calcification is rare." On the other hand

Ribadeau-Dumas (18) states that scar tissue may appear early but that the signs of healing are more frequent in older children.

In this connection Calmette (19) states that "beginning with the age of four years, resistance on the part of the body commences to manifest itself in its disposition to form fibrous tissue and thus to restrict the spread of the tubercles."

O'Brien and Ames (20) made careful studies on 78 children at the Boston Consumptive Hospital. Among these children they found

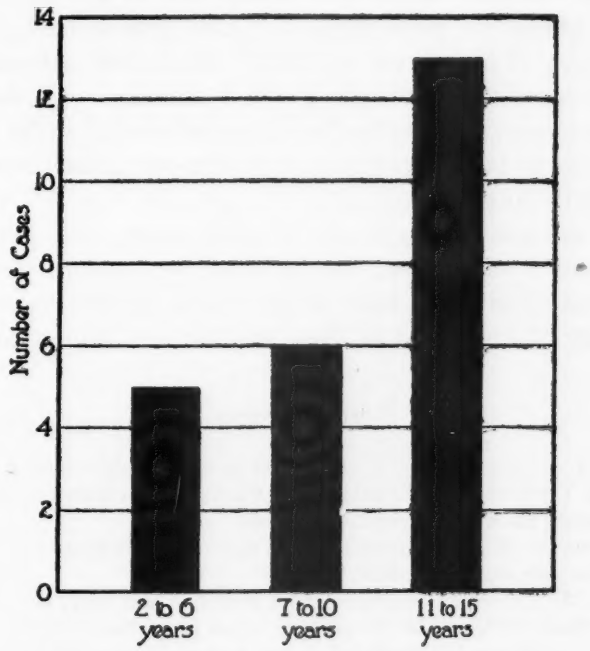

FIG. 1. INCIDENCE OF CHRONIC PULMONARY LESIONS IN THREE AGE GROUPS OF CHILDREN

twenty cases with definite chronic pulmonary tuberculosis. It is interesting to note that 10 of these 20 children were under ten years of age. These authors believe that chronic pulmonary tuberculosis in children is more frequent than it is generally believed to be. Moreover, they conclude that serial roentgenographs should become a routine procedure in the examination of the chests of children.

Griffin (21) from a study of school children in Norwood and Sharon, Massachusetts, came to the conclusion that there is at least one child in

every thousand who has pulmonary tuberculosis. He believes that if a careful study were made there would be found a large number of children in any large city who need sanatorium care.

Among 2000 children examined in the out-patient department of the Lymanhurst School for Tuberculous Children there was a group with definite evidence of diseases of the bronchi. Among these were found a number of cases of bronchiectasis which are being reported by Morse and Lippman (22).

From our total number of cases there were 30 who showed definite evidence of pulmonary involvement. Of these, 6 were due to pneumonia. The remaining 24 cases were considered tuberculous although we were not able to demonstrate tubercle bacilli in all cases. Of these 24 children, the lesions were located in the left upper lobe in 8, in the right upper lobe in 12 and in both upper lobes in 4. In only 4 cases was there evidence of cavity formation.

When grouped according to sex, 18 of our cases, or 75 per cent, were girls. Figure 1 shows that the incidence of pulmonary tuberculous lesions increased with age, there being none in children under two years of age while 54.4 per cent of these children were more than ten years old.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

IV. THE INCIDENCE OF PLEURISY IN 2000 CHILDREN EXAMINED FOR TUBERCULOSIS[2]

J. A. MYERS AND C. O. ROLLIE

Tuberculous pleurisy is said to be quite uncommon in early childhood. Indeed, Calmette (1) says, "Serofibrinous pleurisy is noted but rarely in young children. It does not become common until after the fifth or sixth year and is particularly frequent about the age of twenty years." This is not surprising when one considers that tuberculous pleurisy is a secondary process and the incidence of tuberculous infection is low before the age of six years. It is well known that tuberculous pleurisy is often preceded by a tuberculous lesion in the lung. Some evidence has accrued to lead to the belief that apical pleurisy may result from primary tuberculous lesions in the upper respiratory tract. Again, the pleural lesion may be secondary to tuberculous lesions in the chest wall, in bronchial lymph nodes, in the peritoneum, etc.

Nobel and Steinebach (2) believe that in most cases of pleurisy with effusion in children not recently having suffered from the infectious diseases, etc., the etiological factor is the tubercle bacillus. Their reported series consisted of 78 cases.

Neuland (3) studied 45 children suffering from pleurisy with effusion. He pointed out that it is often difficult to decide whether such processes are tuberculous. After following some of these patients over quite long periods and testing them with tuberculin occasionally, he concluded that quite a proportion of them were not suffering from tuberculous pleurisy.

The prognosis in pleurisy with effusion in children Neuland (3) believes to be much better than that in adults. For example, he points out that in adults with pleurisy with effusion 50 per cent of the cases develop

[1] From the Lymanhurst School for Tuberculous Children, Minneapolis, and the Departments of Internal Medicine and Preventive Medicine, University of Minnesota.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

clinical pulmonary tuberculosis at some later time, usually within five years. Twenty-four of Neuland's cases with positive Pirquet tests were observed from one to ten years after their attacks of pleurisy with effusion. Only two of these developed definite clinical pulmonary tuberculosis and another developed Pott's disease. Eighteen remained perfectly well.

In studying the prognosis in tuberculous pleurisy with effusion in children Nobel and Steinebach (2) observed and reëxamined 39 cases over periods varying from one to nineteen years after the acute attacks. They found that in only 10 per cent of these cases had the pleurisy left marked abnormalities. It is encouraging to know that 41 per cent were completely restored to health and no trace of pleural abnormality could be found by physical or X-ray examination in any of these cases. These authors conclude that the prognosis of tuberculous pleurisy in childhood is usually very good.

Lereboullet (4), in speaking of immediate prognosis, calls attention to the fact that in children under two years of age there is a generalized tuberculosis which of course makes the prognosis grave. In older children, particularly those of or above thirteen or fourteen years, in whom the only evidence of tuberculosis is in the pleura, the prognosis is excellent.

Our work consists of a report of the cases giving histories of pleurisy, together with those in whom definite evidence of pleurisy was found among 2000 children examined for tuberculosis in the out-patient department of the Lymanhurst School for Tuberculous Children. Obviously, not many acutely ill cases would be included in such a group.

Of the 126 children giving histories of pleurisy it was not always possible to determine whether effusion had occurred or, in some cases, whether there had even existed a real pleurisy. This was because of the time which had elapsed since the illness and the fact that some patients tend to exaggerate symptoms and regard every pain in the chest as due to pleurisy. Nevertheless, all who stated definitely that they had had pleurisy were included in our group.

Among the 126 cases giving histories of pleurisy there were only 17 in whom definite evidence of old pleurisy could be elicited by the physical or X-ray examination. From the examination, when the findings were negative, it was impossible to determine whether pleurisy had existed at some previous time, since such lesions may disappear and leave no trace of their former existence. Nobel and Steinebach (2) have pointed out

that fibrous changes in the pleura may undergo retrogression for years and finally disappear, leaving no abnormality whatsoever.

From physical and X-ray examination, 58 of our entire group of 2000 cases showed definite evidence of pleurisy. It is interesting to note that in 44 of these cases neither past nor present symptoms of pleurisy could be obtained. In only four cases was there a history of definite evidence of empyema and in only two was there pleural effusion present at the time of the examinations. The remainder showed evidence of adhesions or definite thickening of the pleura.

It is a well known fact that tuberculosis is not the only cause of pleurisy. Therefore, we have attempted to collect some evidence as to the probable etiology in this group of cases. Although definite histories of exposure to tuberculosis and positive tuberculin tests by no means prove the etiology of a pleural lesion such as those found in our group, we thought it would be of considerable interest to determine the number with histories of contact exposure and positive Pirquet tests. There were 24 of the 58 with evidence of pleurisy who gave definite histories of exposure, while in the remainder there was only questionable or no history of exposure. Among the entire group of pleurisy cases there were 34 who reacted positively to the Pirquet test.

Since pneumonia frequently leaves pleural adhesions in its wake, we have grouped our cases with evidence of pleurisy according to histories of pneumonia. It was found that 22 from the entire group of 58 gave histories of having had one or more attacks of pneumonia. It was also interesting to note that the incidence of measles, pertussis and influenza was very high in this group of cases.

Inasmuch as the lymph nodes of the lung hilum receive lymph from the visceral pleura, and pleural lesions, such as those found in our group, usually involve the visceral pleura, we have attempted to determine whether there is any relationship between the enlargement of the nodes of the hilum and the pleural lesion. Of course, in many of our cases the only evidence of pleural lesions is the presence of old pleural adhesions. Therefore, involvement of the lymph nodes at the time the pleural lesions were acute may have subsided, leaving no evidence obtainable by physical and X-ray examination. On the other hand, severe involvement of the lymph nodes is capable of resulting in much enlargement, fibrosis and calcification, leaving permanent evidence of the involvement by our gross means of examining them in the living body. One must ever be cognizant of the fact, too, that infections of the lungs and the ramifications of the bronchial tubes may result in lymph-node enlargement.

In 7 of our 58 cases there was evidence of enlargement or calcification of the hilum nodes on the side of the pleural lesion, in 32 cases there was such evidence on both sides, while in 7 cases it was found only on the

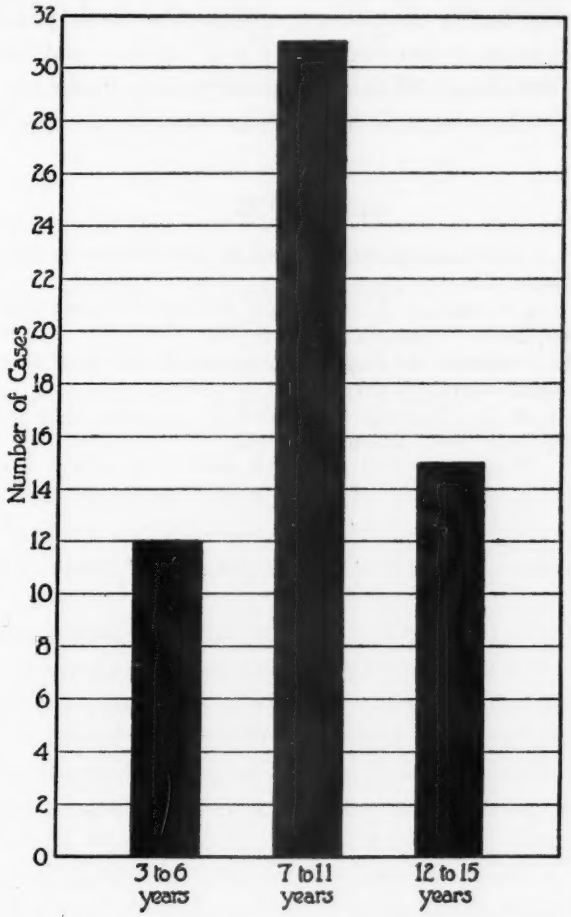

FIG. 1. INCIDENCE OF PLEURISY IN THREE AGE GROUPS OF CHILDREN

opposite side. In the remainder of our cases there was no X-ray evidence of calcification or enlargement of the hilum nodes.

With regard to location of the pleural lesions in our 58 cases, 24 presented their lesions over the left lower chest and 15 over the right lower chest. In 8 cases there was evidence of pleurisy over both lower chests,

while in 6 cases the pleura over the apex of one lung was involved. The remaining cases showed evidence of pleurisy lesions over other locations such as the interlobar region.

When grouped according to age (fig. 1) there were no cases with evidence of pleurisy before three years. From three to six years there were 12 cases, from seven to ten years there were 30 cases and from eleven to fifteen years there were 15 cases. In our group, therefore, the highest incidence of evident pleural involvement was between seven and ten years.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

V. THE RELATION OF TUBERCULOUS INFECTION TO CALCIFICATION OF THE HILUM LYMPH NODES OF THE LUNG[2]

J. A. MYERS AND KUEN TSIANG

It has long been known that calcium deposits in certain parts of the body result from several conditions. One of these conditions is tuberculosis. Wells, DeWitt and Long (1) state that "calcification as it occurs in tuberculous areas does not differ from calcification in any other situation." Again they say, "The chemical composition of the calcific deposits in tuberculosis differs not at all from those occurring in other pathological conditions." It has been shown by Gohn and Winternitz (2) and others that primary tuberculous foci in the lungs usually calcify. Moreover these primary foci are accompanied by caseous foci in the lymph nodes draining them. Subsequent calcification of these lymph nodes is not uncommon, as Ranke (3) and others have observed.

After a thorough-going pathological study, Opie (4) recently concluded that "Active pulmonary tuberculosis (phthisis) is always accompanied by evidence of a preceding tuberculous infection, calcified foci, etc. Calcified foci of healed tuberculosis are present in the lung substance and in adjacent lymph nodes. These calcified lesions found in the lungs of those who die with phthisis are usually less extensive than those found in the lungs of adults who have died from other causes." Gloyne (5) made a careful pathological study of the mediastinal nodes in three nontuberculous and five tuberculous cases. In the nontuberculous cases no calcareous nodes were found, while in the tuberculous cases four calcareous nodes were found, two of which had previously been detected by the X-ray.

Frazer and MacRae (6) raised the question as to whether calcification

[1] From the Lymanhurst School for Tuberculous Children, Minneapolis, and the Departments of Internal Medicine and Preventive Medicine, University of Minnesota.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

of the hilum lymph nodes is indicative of tuberculosis. Occasionally one hears the statement that roentgenological findings interpreted as calcifica-

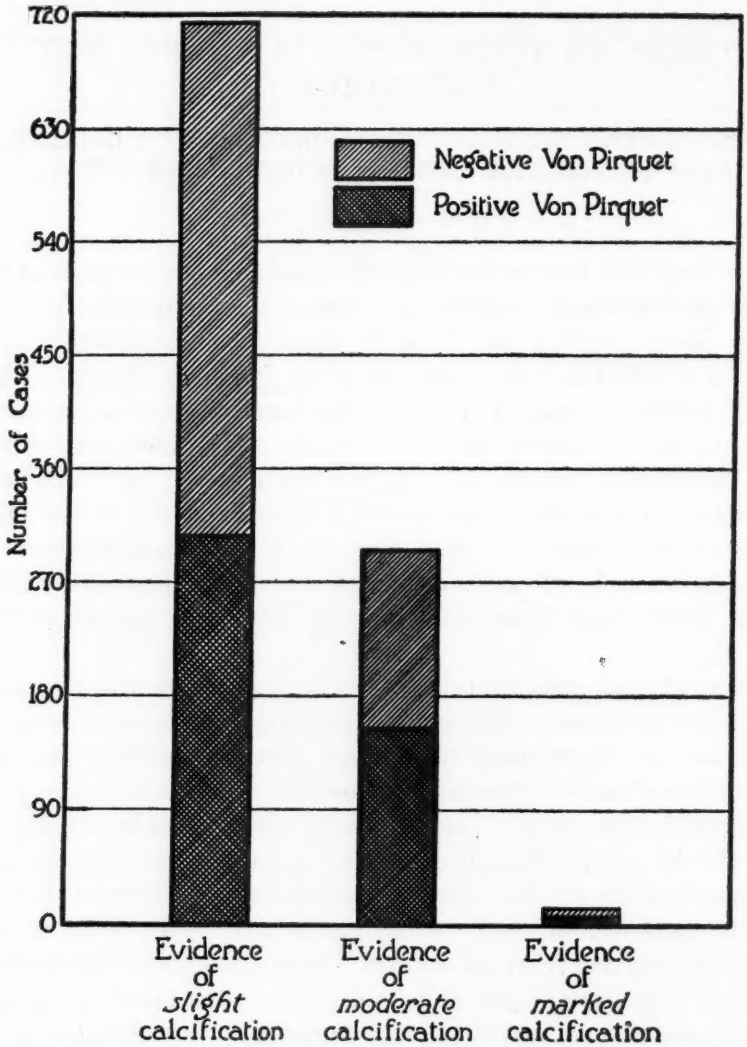

FIG. 1. RELATION OF VON PIRQUET REACTIONS TO CALCIFICATION OF THE HILUM LYMPH NODES

tion of the hilum nodes is sufficient evidence to diagnose tuberculosis of these nodes. It is gratifying to read a definite statement on this subject by no less authority than a committee consisting of Pancoast, Dunham

and Baetjer (7), appointed by the National Tuberculosis Association for the express purpose of studying the roentgenological findings in the chests of normal children. Their statement is as follows: "Calcified nodes at the root of the lung, without evidence of lung disease, are of no significance except as a possible evidence of some healed inflammatory condition, possibly but not necessarily tuberculous. They are a common finding in normal chests."

The material which we wish to present consists of 1412 cases examined in the out-patient department of the Lymanhurst School for Tuberculous

TABLE 1

Calcification of hilum lymph nodes

AGE IN YEARS	SLIGHT		MODERATE		MARKED	
	Pirquet		Pirquet		Pirquet	
	+	−	+	−	+	−
Less than 1	1	0	0	0	0	0
1	1	1	0	2	0	0
2	3	8	0	0	0	0
3	5	15	0	1	0	0
4	20	18	4	5	0	0
5	21	31	0	0	0	0
6	30	39	8	8	1	0
7	33	46	1	5	0	0
8	27	39	26	21	0	1
9	34	41	15	7	0	0
10	34	32	23	18	0	0
11	31	44	13	18	2	0
12	19	24	20	18	1	1
13	15	20	14	11	0	1
14	13	30	19	10	0	1
15	14	19	5	16	2	1
16	2	1	4	4	0	0
17	2	4	1	2	0	0

Children. In 388 of these cases the stereoscopic plates revealed no evidence of calcifications, while in the remaining 1024 cases there were findings which the roentgenologists interpreted as areas of calcification in the hilum lymph nodes. Of these 1024 cases 70 per cent presented evidence of only slight calcification, 29 per cent presented evidence of a moderate amount of calcification, while only 1 per cent showed evidence of marked calcification. Of the total number showing evidence of calcification of the hilum nodes, 45 per cent reacted positively to the Pirquet test. When grouped according to the amount of calcification present

(fig. 1) it was found that 43 per cent of those with slight calcification, 53 per cent of those with moderate calcification, and 54 per cent of those with marked calcification reacted positively to the Pirquet test.

In table 1, it will be observed that only a small number of cases present evidence of calcification of the hilum lymph nodes before the age of four years. Sight must not be lost of the fact that in these early years as well as after fifteen years our number of cases was smaller than in the intervening years.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

VI. D'ESPINE'S SIGN AND STEREOSCOPIC ROENTGENOGRAMS IN THE DETECTION OF ENLARGED HILUM LYMPH NODES IN A GROUP OF CHILDREN EXAMINED FOR TUBERCULOSIS[2]

KUEN TSIANG AND J. A. MYERS

In 1907, and again in 1910 D'Espine (1)(2) of Geneva called attention to a sign among children which he had observed for several years, and which he first thought was diagnostic of tuberculous lymph nodes at the roots of the lungs, but which he finally concluded was diagnostic of enlarged tracheobronchial nodes due to any one of several causes. Morse (3) has called attention to the fact that the sign to which D'Espine originally referred was a whispered sound following the spoken voice and heard over the spinous processes. D'Espine stated that in children whispered bronchophony normally ceased at the level of the seventh cervical vertebra, but that in enlargement of the bronchial nodes it extended downward to the upper thoracic spines. In older children and adults the bifurcation of the trachea is at a lower level than in the infant, and for this reason the bronchophony is of questionable significance unless heard at a lower level. Frazier (4) believes it must be heard below the level of the first and second dorsal spines in a child of eight, and below the level of the third and fourth dorsal spines in a child of twelve. Morse (5) considers the sign positive when the bronchial sound extends below the first dorsal spine. Howell (6) accepts as a positive D'Espine sign a change in the character of the whispered voice or expiration at or below the second dorsal spine.

The transmission of the whispered voice usually indicates that some tissue denser than normal is present between the trachea and bronchi and the anterior surface of the vertebral column which transmits the sound without modification. Experience shows that such tissue is

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[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

usually in the lymph nodes which have become enlarged. Stoll (7) states that D'Espine's sign is indicative of a pathological process at the roots of the lungs, which mostly may be due to enlarged lymph nodes, the results of tuberculosis, malignant tumor, leukemia, Hodgkin's disease, syphilis, or any infectious disease of the lungs. Howell found most of the D'Espine-sign cases revealed a hilum shadow, abnormal in size and density, on the roentgenograms. Morse (5) found 40 cases out of 666 (only 6 per cent) well-to-do children to have D'Espine's sign. He believed that 50 per cent of his positive group were tuberculous, but did not confirm his findings by X-ray or by necropsy. Balyeat (8) concluded his study by stating that D'Espine's sign is indicative of enlarged lymph nodes at the roots of the lungs and, especially when coupled with poorly nourished condition, is usually evidence of tuberculous infection.

Cunningham and Ratcliffe (9), Frischman (10), Smith (11), and Méry (12) are of the opinion that D'Espine's sign is of extreme value in the detection of enlarged hilum lymph nodes, while Langer (13), Moorman (14), Anderson (15), and Fleischner (16) believe the test is worth while but are not so enthusiastic about it. In fact, Anderson believes that this sign is more difficult and is of no greater value than some of the other physical signs of hilum-node enlargement.

O'Brien and Ames (17) found D'Espine's sign present eleven times, while they found X-ray evidence of lymph node enlargement in 28 cases. From their study they believe D'Espine's sign is of relatively little value in the detection of clinical tuberculosis of the bronchial lymph nodes.

Among 300 children examined for tuberculosis Levinson (18) found that 141 reacted positively to the Pirquet test. Of these positive cases 75 per cent showed hilum dulness and whispered bronchophony to the seventh dorsal vertebra. These findings were usually confirmed by X-ray plates showing a shadow over the hilum.

Klare and Dehoff (19) found a general agreement between X-ray plates and D'Espine's sign in 400 cases.

Barlow and Thompson (20) say:

> We have found by special attention to this sign in over 1000 cases that the sign is found in practically every case of early tuberculosis and in the majority of cases of late tuberculosis, and that it is practically never found unless there are present both constitutional symptoms and X-ray evidence of present or very recent active tuberculosis at the hilum. In other words, D'Espine's sign is an evidence not of greatly enlarged tracheo-bronchial glands, but of hilum tuberculosis. A careful study of properly taken stereo-roentgenograms shows

that D'Espine's sign is present only when there is a mediastinal or central pneumothorax, which is, at least in part, at a level which brings it in contact with the trachea. We have never found a clear-cut D'Espine's sign unless there was also a mediastinal or central pneumothorax in contact with the trachea; and, conversely, a mediastinal or central pneumothorax of any appreciable size usually gives a clear-cut D'Espine's sign.

Carroll and Gibson (21), after studying D'Espine's sign and X-ray plates in 411 children, concluded that this sign does not occur indiscriminately. They are of the opinion that the sign should not be disregarded but should be considered as one of the evidences in the diagnosis of hilum tuberculosis.

The committee (22) appointed by the National Tuberculosis Association, consisting of Pancoast, Landis, Baetjer, Dunham, Austrian and Blackfan, reported as follows:

> Concerning the whispered voice sounds, little comment needs to be made other than to emphasize their loud transmission often with syllabation over the region of the major bronchi. Auscultation of these sounds over the upper thoracic spine of the children has led to the conclusion that D'Espine's sign as indicative of enlarged tracheobronchial lymph nodes is, to say the least, of doubtful value. In 23 of the children, this sign was elicited without other signs of a mediastinal mass and without any corroborative evidence on X-ray examination. In 3, the sign could not be elicited, although from the X-ray plate it might have been inferred that it should be. Eustace-Smith's sign is so generally present in normal children that it is of little or no practical diagnostic worth. The presence of these two signs together with impairment of resonance in the interscapular region is all too frequently made the premises for a diagnosis of tuberculosis of tracheobronchial lymph nodes. This is unwarranted for, as indicated, these signs are unreliable evidence of a pathological condition and the determination of a diminution of resonance in the interscapular region requires such a nicety of technique that even masters of percussion disagree as to the presence or absence of significant findings in this region of the chest.

Hawes (23) recently expressed considerable skepticism with regard to the value of D'Espine's sign.

Our group of cases consists of 1057 children examined in the outpatient department of the Lymanhurst School for Tuberculous Children. These children were examined physically by clinicians while the X-ray work was done independently by trained roentgenologists. We were of the opinion that it would be worth while to go through these records and determine how often the presence of D'Espine's sign corresponded with

the roentgenologist's interpretation of enlargement of the hilum lymph nodes. Of this entire group 311 showed the presence of D'Espine's sign, 211 of which (fig. 1) presented X-ray evidence of hilum-node enlargement or calcification or both. The remaining 100 with D'Espine's sign present showed no evidence of hilum-node enlargement or calcification by X-ray examination. The remaining 746 children in our group

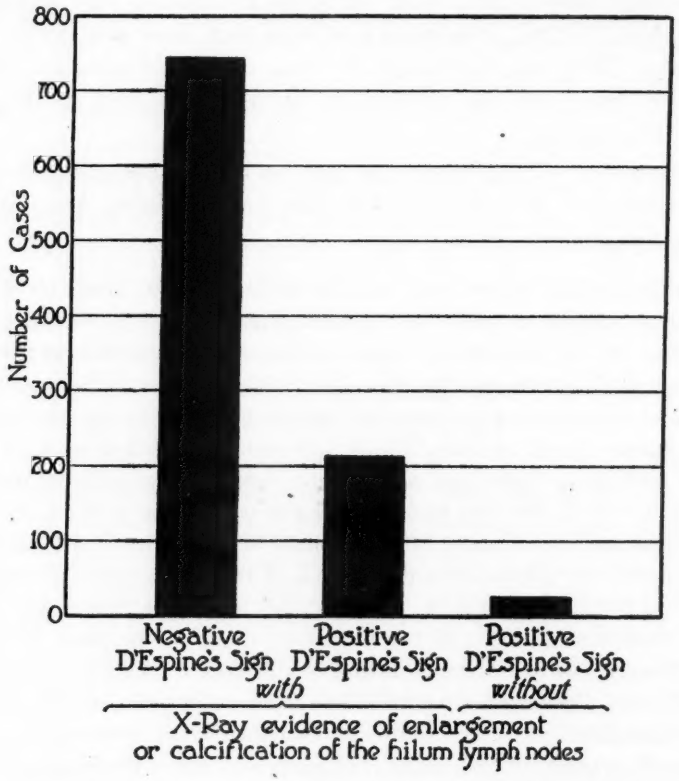

FIG. 1. RELATION OF THE D'ESPINE SIGN TO ENLARGEMENT OR CALCIFICATION OF THE HILUM LYMPH NODES

presented X-ray evidence of slight or moderate enlargement or calcification or both of the hilum nodes but D'Espine's sign was absent. To be sure, one would not expect to find this sign present in cases with only slight enlargement of the hilum nodes.

In table 1 it is noticeable that D'Espine's sign was rarely present in children under five years of age. This may be due to the small number of

cases examined in that period of life. From six to thirteen years of age, the positive-sign cases rapidly increased. Sex, in regard to age, makes little difference. Nevertheless, about one-third of positive D'Espine's sign cases found during the period between six and thirteen years revealed no abnormality in roentgenograms. In a recent paper (24), it was pointed out that more than 50 per cent of cases with X-ray evidence of hilum-node calcification presented negative reactions to the Pirquet test. This fact, as well as the findings of other workers, has convinced us

TABLE 1

AGE	POSITIVE D'ESPINE SIGN WITH EVIDENCE OF ENLARGEMENT OF HILUM LYMPH NODES REVEALED BY X-RAY	NEGATIVE D'ESPINE SIGN WITH EVIDENCE OF ENLARGEMENT OR CALCIFICATION OF HILUM LYMPH NODES REVEALED BY X-RAY	POSITIVE D'ESPINE SIGN WITH NO EVIDENCE OF ENLARGEMENT OF HILUM LYMPH NODES REVEALED BY X-RAY
years			
Under one	3	7	0
2	0	23	2
3	0	33	1
4	4	51	0
5	5	45	3
6	16	67	9
7	23	68	11
8	27	71	14
9	21	57	13
10	14	49	8
11	25	56	16
12	23	58	9
13	12	18	0
14	14	62	7
15	17	60	6
16	2	11	2
17	0	10	0

that D'Espine's sign even when present is not diagnostic of tuberculosis. On the other hand, a negative D'Espine sign does not exclude tuberculosis. We believe that D'Espine's sign should not be omitted from the routine of physical examinations in children but that one should be guarded in drawing any conclusions from the presence or absence of this sign alone. From this study we are convinced that stereoscopic roentgenograms are indispensable in the examination of hilum lymph nodes in childhood.

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PULMONARY TUBERCULOSIS IN A PREGNANT WOMAN TERMINATING IN SPONTANEOUS PNEUMOTHORAX SHORTLY BEFORE LABOR

Report of a case[1,2]

JAMES L. DUBROW

The problem of the treatment of the pregnant tuberculous woman is beset with many complications and the views as to the proper management by no means agree. Pregnancy itself has been regarded as a normal physiological process, but recently DeLee is not so inclined. Its problem with pulmonary tuberculosis resolves itself into many possibilities, all of which must be considered when the two conditions coexist.

For many years there were two distinct opinions as to the proper medical procedure for pregnancy occurring with pulmonary tuberculosis; the one counselled interruption of the pregnancy (the so called German view to which the Italians and Swiss contributed), and the other held that pregnancy exerts no harmful influence on tuberculosis (the so called French view). In 1922 Peham (27) stated that internists in general favor interruption while obstetricians oppose it. The present trend is, however, toward a more careful consideration of the details of the individual case.

LITERATURE

The importance of the subject may be well appreciated from Bacon's estimate (in 1913) of 32,000 tuberculous women becoming pregnant annually in the United States, and the voluminous medical literature on the subject. During the past five years alone articles in the English language on the subject reached a score or more. In the United States Douglass and Harris (1), from a study of 300 cases, concluded that pregnancy is an important factor in lighting up quiescent tuberculosis, and that pregnancy should be avoided until the pulmonary condition has been arrested for several years. When conception has taken place, pregnancy should be terminated before the fifth month in all active cases of early and moderately advanced pulmonary tuberculosis, and in all cases of advanced tuberculosis when the process is quiescent.

[1] From the National Jewish Hospital for Consumptives, Denver, Colorado.
[2] Read before the Denver Sanatorium Association, December 23, 1924.

Walsh (2), remarking on the "German and Italian hysteria," pointed out that a certain number of tuberculosis cases go on to death each year, apart from pregnancy or other complications under the best of treatment. He finally concluded that quiescent cases becoming pregnant, if put on a rigid regimen, may be expected to come through pregnancy with but little, if any, advance of the tuberculosis. Active cases run definite risks, yet the operations for abortion, especially those associated with sterilization, have a mortality that makes the continuation of the pregnancy more desirable.

About this same time (1918) Norris and Landis (3), reporting on 103 cases of pregnancy with pulmonary tuberculosis, believed the latter to exert no influence against conception and but little influence on the course of pregnancy and, except in the advanced stages of tuberculosis, little influence toward causing abortion or premature labor. About 20 per cent of their cases of mild, quiescent pulmonary tuberculosis, and 70 per cent of more advanced cases had exacerbations during pregnancy or the puerperium. They stated that it is impossible to determine with certainty which patients will bear the added strain of pregnancy well and which badly. Patients must be individualized. Moderately extensive lesions, recent activity, secondary lesions, loss of weight, fever, hemorrhage, sweats, lack of vigor and inability to obtain proper treatment, are ill omens. Prior to the fifth month the uterus should be emptied if the disease shows evidences of becoming active, or if the lesions are extensive or laryngeal involvement occurs. Curettage during the first six or eight weeks, and vaginal hysterectomy in the later cases are preferable methods. Interruption does not ensure an amelioration of the pulmonary condition but definitely improves the prognosis. Late intervention gives less satisfactory results. Sterilization is rarely justifiable. After the fifth month expectant treatment is advised. Induction of premature labor two weeks before term is often advisable; rarely should the patients be allowed to go beyond term. At labor forceps or version is usually indicated. It is doubly important that tuberculous pregnant women shall be given the same care as the nonpregnant tuberculous person, as far as rest, hygiene, diet, etc., are concerned.

Elliott (4) practically reiterates the statements by Norris and Landis. Thompson (5) quotes replies received from eleven American tuberculosis specialists who voice variegated opinions on interruption though tending toward conservatism, and finally sums up his own opinion in one sentence as follows: "Pregnancies and deliveries are undesirable and may be dangerous, but abortions are worse. When called upon to choose between the two I advise that pregnancy be permitted to go to term."

In 1922 Norris and Murphy (6) reported on 166 cases, and repeated many of the statements of Norris and Landis with, however, slight modifications. Prior to the fifth month of pregnancy the uterus should be emptied if the disease shows any signs of becoming active. Curettage during the first six or

eight weeks, and vaginal hysterotomy in the later cases are preferable. As to the latter method, while it is preferable from an operative standpoint, it must be remembered that abortion can be induced without a general anesthetic, whereas one is usually required if a vaginal hysterotomy is performed, and sometimes the latter fact will outweigh the advantages of the method. About 65 to 70 per cent of suitable cases will be benefited by this treatment, provided it is employed as soon as acute symptoms arise and proper after-treatment is instituted. Late intervention, that is, after a week or more from the onset of the exacerbation, has given less satisfactory results. Sterilization is not justifiable as a routine procedure. Expectant treatment is advisable after the fifth month of pregnancy.

Slater (7) cited Greer, Minor and Vornveld as reporting favorably on cases of pregnancy undergoing artificial-pneumothorax treatment, and, as a result of his own experience, believed it possible to carry out the treatment on suitable cases with benefit to both mother and child. Pregnancy in itself is not an indication for discontinuing the pneumothorax.

The foreign literature of the past five years on pregnancy and tuberculosis is too exhaustive to permit citing more than a few more important pertinent opinions. Carpi (8) believed that all pregnant tuberculous women should be treated conservatively in sanatoria, and that with reactivation of a one-sided condition artificial pneumothorax should be considered. Baldassari (9), as a result of the study of 88 cases from 1902 to 1913, of which 67 were interrupted, believed interruption of pregnancy to be indicated except in healed cases or those in excellent general condition. The more rapid methods (Krause, Bossi) of interruption are preferred. In florid tuberculosis operative sterilization is justified.

Schweitzer (10), in general, believed in conservative sanatorium treatment during pregnancy and after labor, with artificial-pneumothorax treatment in suitable cases. Laryngeal cases as a whole gave a poor prognosis. Barth (11), who is a laryngologist, did not agree with Schweitzer that all laryngeal cases have a bad prognosis and require interruption. Any good laryngologist can differentiate the favorable from the unfavorable cases. Kehrer (12) found that pregnancy, and especially the puerperium, usually influenced pulmonary and laryngeal tuberculosis unfavorably. If activation occurs during pregnancy immediate sanatorium treatment should be instituted, and if then no improvement takes place the pregnancy is to be interrupted. In the Stage III cases interruption is absolutely indicated but only during the first half of pregnancy. Stage II cases, and Stage I or II cases complicated with laryngeal tuberculosis, require total extirpation of the uterus with interruption. Sanatorium treatment during the second half of pregnancy especially in laryngeal cases is worthless, since 90 per cent die in the puerperium.

Hamburger (13) viewed interruption as favorable to the subsequent course

of the disease. As a result of a study of 101 women, with outspoken active processes aborted before the fourth month, it was believed by Franz (14) that this procedure was justified, although statistical figures did not point to any advantages of the procedure. Rist (15) has been more radical in believing pregnancy a severe, often fatal, complication of tuberculosis, and that most favorable cases have been erroneously diagnosed as tuberculosis. Artificial pneumothorax is the only method of benefit; it does not interfere with the normal course of the labor and delivery. Blum (16), on the other hand, favors the conservative method, and believes pulmonary and laryngeal tuberculosis in themselves no grounds for interrupting the pregnancy. Nubiola (17) believes that, on the whole, pregnancy exerts no unfavorable influence on tuberculosis, so that universal abortion is not indicated. Since progression of the tuberculosis, if it occurs at all, takes place at the end of pregnancy it is advisable to hasten delivery before term. Scherer (18), from a study of 2,777 women, among 8,520 tuberculous women and children of the Kronprinzessin Cecilie Sanatorium, who passed through 8,198 pregnancies, concludes that pulmonary tuberculosis does not pursue a more unfavorable course during pregnancy than in its absence. Repeated successive pregnancies, in some cases 13 to 19, were noted, and are not rarely unfavorable. Interruption is justified only exceptionally, and the danger of abortion itself must then be recognized, since the child may be sacrificed without benefiting the mother. Outspoken laryngeal tuberculosis is looked upon as an indication for interruption. Artificial sterilization may be desirable when repeated pregnancies demand it.

Many French authors, including Thiroloix (19), Bar (20), Hergott (21), Sergent (22) and Fruhinsholz (23), are guided entirely by the individual case, and follow the general rule of permitting the pregnancy to go to term unless the general condition of the patient would absolutely dictate otherwise. They consider whether interruption offers any hope of saving the mother, and if it does not they make every effort to save the child by carrying it to term. Poltronieri (24) found that instrumental interruption during the first three months of pregnancy produced no harm to tuberculous women but was not without danger later. After pointing out the hazards of abortion after the fourth month, Bufalini (25) advocates artificial pneumothorax and conservative treatment. Anderodias and Monod (26), because of a disastrous experience in three fatal cases of tuberculous laryngitis, in which interruption resulted in the loss of the children without in any way benefiting the mothers, advise against such a procedure, and that all effort should be exerted in saving the child.

Peham (27) of Vienna, Schumacher (28) of Giessen, Winter and Oppermann (29) of Königsberg, P. Strassmann (30), Waldstein (31), and Weymeersch and Albrechts (32) view the problem much as do Norris and his colleagues.

It is interesting that, in spite of the voluminous literature on pregnancy

and tuberculosis and on spontaneous pneumothorax, no report was found in which spontaneous pneumothorax had occurred during pregnancy. It seems within reason that spontaneous pneumothorax should occur, especially during the strain of delivery, and in advanced cases of pulmonary tuberculosis, but the gravity of other conditions may have overshadowed it to the extent that it is commonly overlooked. That pneumothorax itself cannot be detrimental to pregnancy is evidenced by the favorable reports on this treatment and by Castelli's report (33). In a patient in the second month of pregnancy an artificial pneumothorax was instituted for acute tuberculosis of the upper lobe of the right lung. Fever and cough subsided and weight rapidly increased. Delivery was normal and the child was artificially fed. Pneumothorax was maintained for some time after delivery. It is noted that the interruption of pregnancy in even severe cases should be cautiously undertaken. Hervé (34) holds this same opinion, and reports two cases in which pregnancy and delivery were uneventful with an existing artificial pneumothorax. He concludes that one respiring lung suffices for the pregnant woman, and in the presence of pneumothorax pregnancy need not be interrupted. In the American literature Marshak and Craighead (35) in 1918 stated that "to one familiar with the pneumo-mechanics of the chest, it seems that spontaneous pneumothorax during the course of an induced pneumothorax should be a rather frequent complication. The literature, however, shows rather few reports despite the large number of cases. That it may have been overlooked, or the symptoms ascribed to other complications, are probable reasons for the infrequent reports."

Heise and Krause (36), after commenting on spontaneous pneumothorax, state that "while, on theoretical grounds, rupture of the lung as a consequence of induced pneumothorax should occur fairly frequently, we must nevertheless at present regard it as one of the rare complications of the procedure. When it happens, the diagnosis should not be difficult to make; and if it really happened often we would have more reports of it."

Cocke (37) reports a case of spontaneous pneumothorax following artificial pneumothorax in a man with chronic diffuse tuberculous bronchopneumonia. Under local anesthesia a rib was removed and a drain inserted to treat the pyopneumothorax, and the recovery was phenomenal with complete healing in one year. Kahn (38) adds four cases to the literature in 1921 and warns against too great pressure in artificial pneumothorax. In another article (39) he decrys the high mortality rate (80 per cent) in spontaneous pneumothorax, and believes that it should not exceed 10 per cent and that of the other 90 per cent at least 40 to 60 per cent should derive actual benefit from its occurrence.

Morris (40) in a rather exhaustive review of the literature, found that tuberculosis is the cause of spontaneous pneumothorax in from 30 to 90 per cent of the cases, and that opinions differ as to the frequency of spontaneous

pneumothorax in tuberculosis, the figures varying from 0.1 to 13 per cent. His own series revealed 2.64 per cent of 636 cases of tuberculosis.

The treatment of spontaneous pneumothorax, according to Hayes (41), is symptomatic. As far as possible, interference should be avoided. In cases showing improvement following the pneumothorax, in which expansion tends to take place, compression should be maintained. This may be accomplished to a certain extent by fluid in those cases in which it occurs. The method of choice is, however, by the introduction of air. This is possible only when the original opening has closed. If fluid is present the air is introduced after aspiration. The objections to allowing the fluid to remain are (1) that even when reported sterile it may give rise to toxic symptoms; (2) that it may occasion pressure symptoms, which may be present when there is not more than a pint of fluid in the pleural cavity; (3) that infection of the fluid is very likely to take place; and (4) that when the fluid is present adhesions, which tend to pull the lung out, form more readily. When the collapse of the lung is fairly complete and the mediastinum is not fixed by adhesions, so that its displacement with compression of the other lung gives rise to severe symptoms, as happens in the cases with valvular openings, repeated aspiration of the accumulated air affords marked relief. When the reaccumulation of the air takes place rapidly the insertion of a small cannula in the chest wall, which may be left for a period of days, may better serve the purpose. When pyothorax supervenes and the original opening is closed, very satisfactory results in clearing up the infection in a large percentage of cases may be accomplished by repeated aspirations of the pus, followed by the injection of two per cent formaldehyde-glycerine solution.

Weber (42) believes that 80 or 90 per cent of all cases of nonartificial or nonsurgical pneumothorax are associated with tuberculosis, and that generally these patients do not recover. Occasionally tuberculous seropneumothorax recovers without the effused fluid becoming definitely purulent. Spontaneous pneumothorax is a rare complication of pulmonary tuberculosis, according to Barth (43), and for this reason it is frequently not diagnosed early enough. In spite of the fact that spontaneous pneumothorax is a serious condition, careful observation and proper treatment may achieve good results. Valvular pneumothorax on account of the resulting cardiac embarrassment is unfavorable and a prolonged open case, on account of the pleural infection, has also a poor prognosis. The most favorable cases are those that have a simple closed spontaneous pneumothorax, which may even be beneficial.

Among 12,303 consumptives treated by Lucius Spengler (44) there were 42 cases of spontaneous pneumothorax, 18 of these developing in Davos and 16 of prior standing. Of the 42 cases Spengler was able to obtain a cure in 16 (38 per cent), of which 9 are still alive from one to 30 years afterward and 7 are entirely well. Of the 16 cases the pulmonary tuberculosis itself healed

in from 3 to 30 years. Death occurred in 4 of the fatal cases from acute valvular pneumothorax in from 2 to 7 days, and 15 cases within 2 weeks to 2 years, in one after four years and one after eight years. Closure of the pulmonary fistula is requisite to healing. Only with slightly altered pleura does the fistula close without exudate formation. In such cases the procedure is as in artificial pneumothorax. The formation of an exudate has a favorable influence. Withdrawal to a negative pressure to avoid a thoracic fistula from pressure of the exudate into the needle path is advised. The needle is disinfected before withdrawal by the injection of 5 to 10 cc. of iodoform oil or 1 to 2 cc. tincture of iodine. Purulent exudates are to be treated the same as those complicating artificial pneumothorax, by rinsing with iodine-potassium iodide. If no results are obtained thoracotomy and thoracoplasty are to be considered. In cases of dry pneumothorax it is advisable to transform this by injecting 30 cc. of 1 to 2 per cent silver-nitrate solution or, better, 30 to 100 cc. of 30 per cent (or 40 to 50 per cent) glucose-sodium chloride solution, to favor healing of the spontaneous pneumothorax.

Emile-Weil and Isch-Wall (45) obtained excellent results in valvular pneumothorax by the intrapleural injection of *Gomenol*, which can be withdrawn after closure of the fistula, and by air used to continue compression.

Although, as noted in the review of the literature, there have been decided differences of opinion regarding the proper procedure when pregnancy complicates pulmonary tuberculosis, yet, if one is guided by the better experience of the majority, the course is fairly well outlined and can be adapted to the exigencies of the individual case. So also may we sum up the views on spontaneous pneumothorax, and not be guided by the opinion of an occasional individual with only a few cases to his record. While the case to be reported is only a single instance its rarity and complexity would seem to be worthy of record, since it combines not only pregnancy and tuberculosis but also spontaneous pneumothorax.

The patient was a married primipara, 21 years of age, admitted to the National Jewish Hospital for Consumptives, November 28, 1923. She had had typhoid fever in 1913 and influenza in 1922. Menstruation was regular every 28 days, and lasted 4 to 5 days, until six months before admission to the hospital. Symptoms of pulmonary tuberculosis, loss of weight, languor, cough with profuse expectoration and afternoon elevation of temperature following frequent colds, began four months prior to admission.

Physical examination revealed a well-developed and fairly well-nourished young woman, 5 feet, 2 inches tall, weighing 117 pounds and with a hectic flush. The tonsils were irregular and submerged, and there was a mucopuru-

lent secretion on the floor of the right posterior nares. The central margin of the epiglottis was thickened and the thyroid slightly enlarged. Respiratory mobility depressed on left side, and supra and infraclavicular spaces depressed on both sides. Thoracic wall droops on left side, and shoulder depressed. Apex beat displaced to left and visible in third to fifth interspaces. On palpation the vocal and whispered fremitus were exaggerated down to the fifth interspace on the left side, both anteriorly and posteriorly, and to the third interspace on the right side. Percussion elicited marked dulness, with resistance to the pleximeter finger over nearly the whole left side, with the exception of a circumscribed area of hyperresonance in the left third interspace anteriorly and a corresponding area posteriorly. Auscultation revealed cavernous and amphoric breathing, with large and medium râles on the same side. Below the fourth to the sixth interspaces the breath-sounds were bronchial, and below this they were almost absent because of thickened pleura. On the right side only a few crackling râles were heard at the apex. The heart findings were normal except for a diffused apex beat and accentuated second pulmonic sound. The breasts were moderately increased in size, with slight venous engorgement. The nipples were enlarged and deeply pigmented, and colostrum exuded on pressure. *Striae gravidum* were present. The abdomen was enlarged, and the umbilicus smooth and protruding. The fetal heart was heard in the lower left quadrant, and movements were perceptible, while different parts of the fetus could be palpated. The extremities were negative, except for the presence of enlarged and conspicuous veins on the right thigh and the calves. The fingers were not clubbed.

On admission, temperature, pulse and respiration were 99.4°, 96 and 22. The patient was ambulant, and felt well, but had frequent micturition. She had no nausea or morning sickness. The laboratory findings were *w.b.c.* 17,600, *r.b.c.* 5,180,000, hemoglobin 85 per cent, and polymorphonuclears 81 per cent, Wassermann negative, urine normal and 1200 cc. in 24 hours, sputum was mucopurulent and positive for tubercle bacilli.

X-ray and fluoroscopic examination corroborated the physical findings in that there was an extensive fibrosis with inflammatory infiltrations over the entire left lung, with probable cavity in the upper lobe and a thickened pleura over the lower lobe. There was considerable peribronchial thickening throughout the right lung with marked infiltration of the hilum on both sides.

On account of the opposition of both the patient and her husband to interruption of the pregnancy it was permitted to pursue its course.

Aside from a few days of indisposition the patient enjoyed relatively good health, was ambulant, and went to her meals during the first twelve weeks of sanatorium residence. During the ninth month of pregnancy she was ordered to be confined to bed, as a prophylactic measure, and because the exact date of last menstruation was unknown. Repeated urinary examinations during this

period were negative. The later chest examinations disclosed a tendency to fibrosis with fewer râles.

About five weeks after the patient was put to bed she complained of pain in her chest following a mild coughing spell the night before (April 11). Dyspnea and chills developed, and when seen by the physician her facial expression was quite anxious, and she was flushed and cyanotic. Temperature, pulse and respiration were 102°, 126 and 26. Her respiration was superficial in character. Thoracic pain was marked. The left side was almost immobile during respiration. The apex beat was noted at the right fifth interspace about ½ inch inside *m.c.l.* Vocal fremitus was almost absent on the left side and increased on the right. Instead of the previous dulness on the left side the chest was tympanitic down to the seventh interspace. The cardiac dulness was obliterated on the left and displaced to the right. Metallic tinkling was noted in the upper portion of the chest on the left, and there was an absence of breath-sounds. A diagnosis of spontaneous pneumothorax with complete collapse of the left lung was made.

The patient slowly but progressively became worse, and the cyanosis increased and became more generalized, extending to her hands and feet which were cold and clammy. Temperature, pulse and respiration at 11:30 A.M. were 102.6°, 120 and 30; at 1:00 P.M., 102.6°, 146 and 42. Four hundred cubic centimetres of air were withdrawn from the left chest at 1:00 P.M.: initial pressure 0, +1; final reading, − 1½, − 2½. There resulted a distinct abatement of the respiratory and cardiac embarrassment, and the cyanosis completely disappeared, after which the patient rested comfortably for a few hours. At 4:00 P.M. she experienced cramp-like pains in the lower abdomen, extending downward to the thighs and recurring at intervals.

Examination now revealed an irregular breech at the fundus, with resistance of the back in the left and anterior portion of the abdomen and the small parts on the right side. The head was fixed in the superior strait and the cephalic prominence was on the right side. The fetal heart sounds were heard distinctly in the left lower quadrant. On vaginal examination the cervix was found softened, and it admitted the tip of the index finger, verifying the diagnosis of *L. O. A.*

Uterine contractions became increasingly intense, with accompanying distress in breathing and accentuation of cyanosis. Upon advice of the consultant obstetrician the patient was prepared for delivery, but at 7:00 P.M. all uterine contractions ceased, and forcible dilatation of the cervix or caesarean section was considered. A prompt decision was imperative because of the increasing hyperpnea, dyspnea and cyanosis, while respirations increased to 48 and the pulse to 150. In favor of immediate evacuation of the uterus were the prospects for delivery of a living child, and the possibility of decreasing the dyspnea and cyanosis by allowing more room for expansion of the lung.

Against it was the saving of the mother's life, since she was in poor condition to operate. The conservative method was finally chosen especially since the patient again began to have labor pains. Upon examination at this time (10:00 P.M.) the cervix admitted two fingers. There was, however, no marked increase in frequency or intensity of the labor pains during the night. The patient slept at intervals until 2:30 A.M. when dyspnea and cyanosis became so urgent that 600 cc. of air had to be removed. Initially the reading was $+2\frac{1}{2}$, $+\frac{1}{2}$, and finally -2, -4. At 5:00 A.M. another 500 cc. was removed,—initial reading $+1\frac{1}{2}$, $+0$, final -2, -3. About 9:00 A.M. (April 12), after rupture of the membranes, labor was hastened, and an easy delivery, with low forceps by Dr. Burns, followed at 10:30 A.M.

After delivery the patient rested well, and her temperature dropped 1.5°. The next morning, in answer to an emergency call, 500 cc. of air were again aspirated. Temperature, pulse and respiration at 9:00 A.M. were 100.6°, 142 and 36, and at 11:30 A.M. 102.8°, 150 and 48. At noon (April 12), cough and dyspnea being marked, another 600 cc. was withdrawn,—initial reading $+2$, $+1$, final reading -2, -4. Codeine was given for the cough, oxygen inhalation for the dyspnea, and digitalis for the heart.

It is quite evident that the pneumothorax was valvular, since mild coughing spells resulted in a distressing hyperpnea, cyanosis and cardiac embarrassment despite digitalis treatment. The intrapleural tension was positive following coughing spells, regardless of whether aspiration had been performed a short time before. Repeated aspirations were performed, and on April 19th the patient was relatively comfortable. The breasts were allowed to dry, and on the eighth day after delivery the temperature, pulse and respiration were 104°, 142 and 40. At this time the lochia showed Staphylococcus albus on culture, although the puerperium had been normal during the first few days. Leucocytes were 12,400, with 83 per cent polymorphonuclears. Urinanalysis had been negative before delivery. The urine now amounted to only 800–900 cc. in 24 hours, in spite of forced water drinking and the administration of sodium bicarbonate; specific gravity 1024; reaction acid despite sodium bicarbonate administration; albumin, urochromogen, diazo and indican positive; urea content per cubic centimetre 0.0324 (a relative urea increase); and many hyaline and granular casts were present.

The negative urinary findings throughout pregnancy would indicate that the nephritis was not a consequence of the pregnancy but rather of the spontaneous pneumothorax. Slight edema of the eyelids and swelling of the lower extremities developed on April 23rd, with drowsiness, semiconsciousness and mental aberration. There was at this time a tendency to closure of the pleuro-pulmonary valve, as evidenced by the decreasing intrapleural tension when tested. Blood analysis demonstrated renal failure, in that the nonprotein nitrogen was doubled, urea nitrogen increased, and creatinin increased.

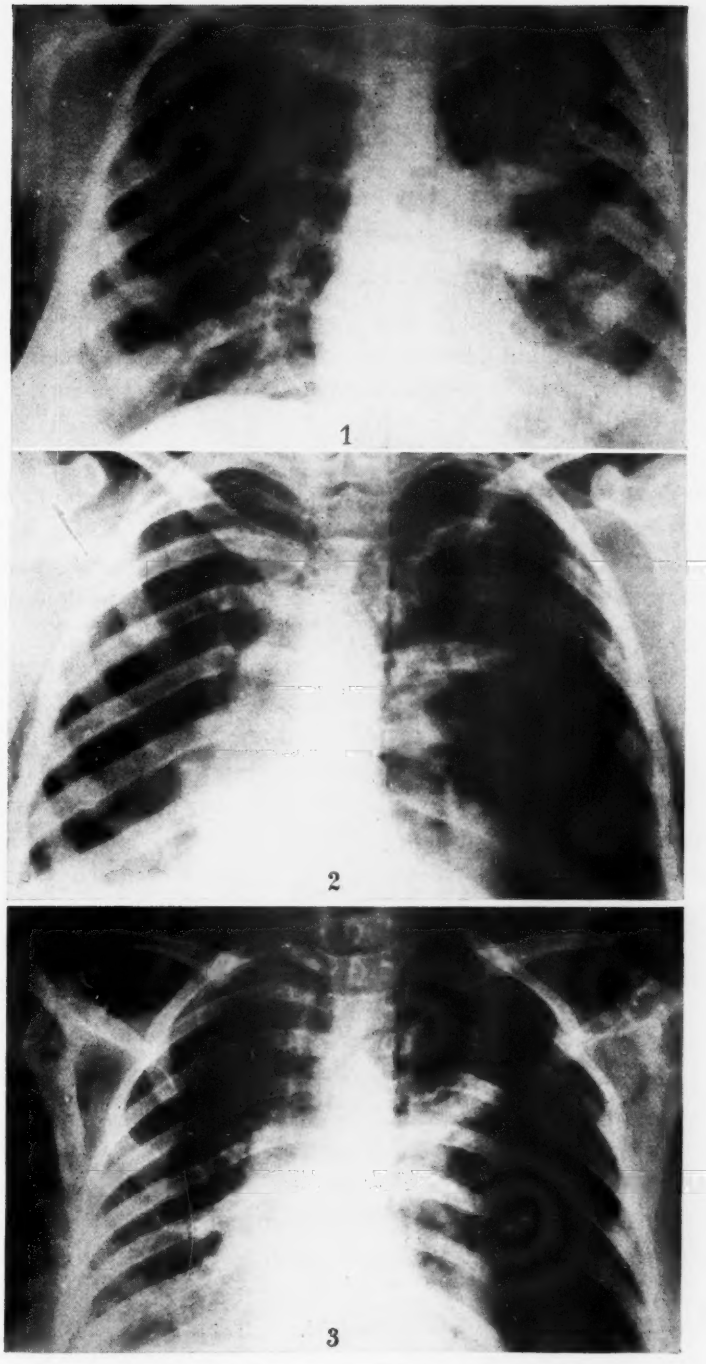

FIG. 1. FIVE MONTHS BEFORE DEVELOPMENT OF PNEUMOTHORAX
FIG. 2. SHORTLY AFTER DEVELOPMENT OF PNEUMOTHORAX AND BEFORE ONSET OF LABOR
FIG. 3. ONE DAY AFTER DELIVERY

The patient died on April 27th (15 days after delivery). Autopsy was refused. The child, artificially fed from birth, weighed 13 pounds at seven months, showed no signs of tuberculosis, and was normal in every respect.

DISCUSSION AND SUMMARY

1. Pregnancy complicated by spontaneous pneumothorax is no doubt a rare condition. It would seem that the strain and stress of delivery would at least lead not uncommonly to the production of a spontaneous pneumothorax in advanced pulmonary tuberculosis, yet such does not seem to be the case. As a matter of fact, the case reported passed through normal delivery (except for the low forceps at the end) in spite of the spontaneous pneumothorax. The paucity of recorded cases of spontaneous pneumothorax complicating pregnancy may be due to oversight; and more careful observations on the pregnant tuberculous woman for this complication are desirable, especially in the later stages of pregnancy and during delivery.

2. The case reported above was a young primipara with advanced pulmonary tuberculosis in whom spontaneous pneumothorax developed on the day of the onset of labor. Permission to interrupt pregnancy during the early months had been denied, and the onset of labor shortly after development of a valvular spontaneous pneumothorax determined the immediate course, in spite of the distressing and dangerous symptoms. A practically normal labor resulted and a healthy child was born, which subsequently showed no signs of tuberculosis. The child was not nursed by the mother and developed normally. The mother succumbed fifteen days after delivery; not, however, from the tuberculosis or the complicating spontaneous pneumothorax, but as the result of renal incompetence which became evident eight days after delivery.

3. It seems that in this case, at least, the conservative method of treating the pregnancy resulted in no evident harm, since a normal child was delivered and the prognosis for the mother with valvular pneumothorax was bad in any case. Whether the pregnancy directly influenced the development of the spontaneous pneumothorax remains undetermined.

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STUDIES ON TUBERCULOUS INFECTION[1]

X. THE EARLY DISSEMINATION OF TUBERCLE BACILLI AFTER INTRACUTANEOUS INOCULATION OF GUINEA PIGS OF FIRST INFECTION

HENRY STUART WILLIS

The series of events after the subcutaneous inoculation of tubercle bacilli into the groin of guinea pigs is definite and uniform. The superficial inguinal lymph nodes become enlarged, firm and shotty, usually within ten days of the inoculation. Very soon after this there are gross signs of involvement of the iliac and paraortic nodes, the infection having spread thus far by the lymph channels. Beyond this point bacilli reach the *receptaculum chyli*, the thoracic duct, the venous blood and lungs, and thence may be carried arterially to any portion of the body, and especially to the spleen. From the lungs they readily reach the tracheobronchial lymph nodes by way of the pulmonary lymphatics, and the tendency is for bacilli to proceed toward these nodes from any part of the body by a continuous path that includes lymphatics, venous system, pulmonary artery and pulmonary lymphatics. But the spread to deep tissues of the body occurs much more rapidly than observation of the various tissues in the gross would indicate. At four days after subcutaneous inoculation, the iliac and tracheobronchial nodes, spleen and lungs contain tubercle bacilli in varying numbers, usually before they are histologically demonstrable. That is to say, bacilli may within four days make the complete circuit of the body, and in doing this spread through a relatively long and obstructed lymphatic pathway, reach the blood, and through this become widely disseminated throughout the body.

The work reported in this paper, growing out of the above observations by Krause (1), represents an effort to learn more about the dissemination, especially the very early dissemination, of tubercle bacilli. It seemed important to learn (1) whether bacilli are transported from the site of introduction *very early* (within hours) after they are put into the

[1]From the Kenneth Dows Fund for the Study of Tuberculosis, of the Medical Clinic of the Johns Hopkins Hospital and University.

tissues; (2) if they are, just how long is required for such migration to get under way; (3) how rapidly the bacilli are moved along the natural avenues of dissemination; (4) where they are carried; (5) what may be their rate of transit from point to point, from inoculation site to axillary or groin lymph nodes, and from these stations to more interior locations; and (6) whether tuberculous infection may be similar to syphilitic infection in that dissemination is very early, and bacteremia, however slight and transitory, the rule. The experiments performed to investigate these questions have consisted of two main parts:

(1) *The enucleation of the sites of inoculation* (*skin*) at varying intervals after infection, *and the subsequent observation of the same animals for the appearance of internal tuberculosis.* If the technique of removal of the sites of inoculation were good, a nonappearance of such infection later would prove that within any specified time bacilli had not progressed beyond the site, while a development of infection would show that bacilli had made this transit.

(2) *The excision of lymph nodes draining the sites of inoculation* at varying intervals after intracutaneous infection and the *inoculation of these nodes into normal guinea pigs.* If any of the latter developed tuberculosis, it would show that they had received bacilli which had travelled from the sites of inoculation to the regional lymph nodes within the time between infection and removal of lymph nodes. On the other hand, absence of infection would prove that, up to the time of removal of the lymph nodes, the bacilli had not progressed so far from the site of inoculation.

1. ENUCLEATION OF AREAS OF INOCULATION

Technique: Thirty normal guinea pigs were inoculated intracutaneously in the side at a point half-way between axilla and groin, each with 0.1 cc. of a thin emulsion of human tubercle bacilli of average virulence (H37). The area of inoculation was washed with cresol and enclosed within a ring of carbol-fuchsin immediately after inoculation was performed. Beginning at one hour after infection, and at every hourly interval up to six hours, and again at ten and at twenty-four hours, and at irregular intervals from two to fifty-six days thereafter, two animals were at each time subjected to the following procedure: With the animal under ether, the site of inoculation was washed with 70 per cent alcohol, and an alcohol sponge was held on the area for

approximately one minute, when the alcohol was washed off with sterile water. The area was then lifted up with sterile forceps while, with sterile scissors, a disc of skin 15 to 18 mm. in diameter (the point of inoculation being its centre) was excised. The area of excision was immediately covered with celloidin. The animal was under ether for about two minutes.

Because of the possibility of contamination of the field of inoculation scrupulous care was taken to avoid error of any kind. At the time of inoculation the point of puncture of the needle was carefully washed with cresol. Great care was taken to prevent a *subcutaneous* instead of an intracutaneous inoculation and occasionally, when the needle was introduced by mistake beneath the skin, note was made of the matter and the animal's record was kept separate from those of the others. It is hardly possible, too, that in any considerable number of inoculations the needle should have got into a cutaneous vein and thus occasioned an intravenous inoculation. The fact, also, as will be shown later, that bacilli were demonstrated in the axillary and inguinal lymph nodes twenty-four hours after the intracutaneous inoculation, is positive proof that dissemination occurs rapidly. Even if one should grant that bacilli contaminated the skin at the site of inoculation, either such extraneous bacilli or the inoculated bacilli must have traversed, in the twenty-four-hour period, the distance between the site of inoculation and the axillary or inguinal lymph nodes, inasmuch as bacilli placed in the skin were recovered twenty-four hours later in the regional lymph nodes, 5 cm. and more, distant. Again, the fact also that the excision wound healed promptly, and in only four animals became the seat of tuberculous ulcer, is evidence that all bacilli were removed. Furthermore, it was found that within the first few hours after inoculation, the very time when most contamination might be expected to occur, operation in numerous animals removed all bacilli, while with increasing time it did not. If contamination of the skin had occurred, the contaminating bacilli would have stood a much better chance of being carried into the cut tissues early after inoculation than later. This is good evidence that contamination of the outlying skin played no important part in the results obtained in the experiment.

After the operation each animal was observed at frequent intervals, to determine the appearance and development of changes in the lymph nodes in the axilla and groin on the side of the inoculation. Any charac-

teristic changes in these would give evidence of infection by tubercle bacilli, and, if this occurred, the time of its appearance after operation could be noted.

Striking results appeared very early. Nearly all of the animals developed enlargement of the regional lymph nodes in the time and manner characteristic of tuberculous infection and at autopsy showed visceral tuberculosis, irrespective of the time of excision of the site of inoculation. Enlargement of the lymph nodes developed uniformly and progressively; earlier in those animals in which the excision had occurred a longer time after inoculation and later in those in which the time was shorter. Once palpable, the lymph nodes rapidly became quite large. It was nothing short of astonishing to note that one animal, which had had its site of inoculation removed *one hour after infection*, gradually but definitely went on to generalized involvement. These results are presented in table 1, in which alternate animals are listed.

Analysis of table 1: It will be instructive to look first at the animals listed toward the bottom of the table. These are the ones in which no excision was made until quite late and they may be considered, therefore, up to the date of operation, as "unoperated" controls to the "operated" animals. Enlargement of the regional lymph nodes was noticeable at the ten-day examination in all animals except those which were operated on within seven days of the inoculation. At fourteen days after inoculation nearly all of the group and by twenty-five days all but one (no. 33, operated on three hours after inoculation) showed extension which was progressive. Of the 30 animals, this and one other (no. 32, operated on at one hour) were the only ones which failed to develop extension of infection. These two animals failed to react to tuberculin, showing that in all probability all bacilli were removed by the excisions and that none got beyond the area of excision in this time. Moreover, the animals were found to be free from tubercle at autopsy.

It is evident from the results shown in table 1 that some of the bacilli were moved from the site of inoculation very promptly after their introduction. But the animals so far studied had their excisions performed at one, three, six, etc., hours after inoculation, and it was desirable to study more closely the dissemination in these early hours after inoculation. In order to obtain further data on this point, 24 normal guinea pigs were given intracutaneous inoculations of an emulsion of H37, as nearly as it could be made like the emulsion used before, and the areas of inoculation (15 to 18 mm.) were excised in four of the animals every

hour from the first to the sixth after inoculation. Two were kept for controls and were not operated on. The animals were examined at frequent intervals for signs of dissemination (enlargement of regional nodes). Of these 24 animals only 5 (two operated on at one hour, two at two hours, one at three hours after inoculation) did not develop signs

Normal													
	Time between inoculation and excision	Days since H37 inoculation										Autopsy	
		7	10	14	18	22	25	30	35	40	55	Nodes	Viscera
31	1 hour	o	o	+	+	++	+++	+++	+++	+++	+++	+	+
33	3 hours	o	o	o	o	o	o	o	o	o	o	o	o
35	6 „	o	o	o	o	o	++	++	++	++	++	+	+
37	10 „	o	o	+	++	++	++	++	+++	+++	+++	+	+
39	24 „	o	o	+	+	+	+	+	+	++	++	+	+
41	2 days	o	?	?	+	++	++	++	++	++	++	+	+
43	4 „	o	o	++	++	++	++	++	++	++	++	+	+
45	7 „	o	+	+	+++	+++	+++	++++	++++	++++	++++	+	+
47	10 „	o	+	++	++	+++	+++	+++	+++	+++	+++	+	+
53	14 „	o	+	+	++	+++	+++	+++	+++	++++	++++	+	+
55	18 „	o	+	++	++	++++	++++	++++	++++	++++	++++	+	+
56	22 „	o	+	+	+	++	++	++	+++	+++	++++	+	+
57	25 „	o	+	++	++	++	++	++	++	++	++++	+	+
58	30 „	o	+	++	+++	++++	++++	++++	++++	++++	++++	+	+
59	56 „	o	+	++	++++	++++	++++	++++	++++	++++	++++	+	+

TABLE 1. SHOWING RESULTS OF EXAMINATION OF ANIMALS AT FREQUENT INTERVALS AFTER INOCULATION AND EXCISION, AND ALSO RESULTS FOUND AT AUTOPSY

Results of examination of inguinal and axillary lymph nodes on the side of intracutaneous inoculation, at intervals up to fifty-six days after inoculation. Alternate animals are charted. The dotted line represents graphically the time of excision in relation to the time of observation of the animal. Further description is given in the text.

of extension during the ensuing forty-three days after inoculation. Three of them gave no reaction to tuberculin, a fourth (operated on at three hours) gave a questionable reaction and the fifth one died without visible tubercle at autopsy. The data of this experiment are presented in table 2. The plus signs represent extension to the lymph nodes of

either axilla or groin; these are about equally divided. It would appear from this table that, under the conditions of the experiment, *it is the exceptional guinea pig in which bacilli do not spread from the site of inoculation within an hour or two of their introduction* and that *the rule is to find a rapid dissemination of bacilli from the involved area.*

Analysis of table 2: It will be seen from this table that the animals operated on at one, two and three hours after inoculation (nos. 1 to 12) showed no signs of extension during the first fifteen days after inoculation, but that gradually most of these animals showed extension. Of the 5 which showed no extension, two were operated on at one hour after inoculation, two at two hours and one at three hours. Three of these (nos. 4, 8 and 12) were large animals with thicker skins than the others. The animals that had received the inoculation four hours or longer before operation all developed tuberculosis, and most of them developed it early. The earliness or lateness of the development of extension no doubt represents a larger or a smaller number of bacilli that had escaped from the field of inoculation before excision. The two "non-operated" controls (nos. 19 and 24) developed lesions essentially like those in the animals operated upon five and six hours after inoculation.

The two experiments showed plainly that all the bacilli did not remain fixed and dormant for hours or days at the sites of inoculation, but that they were transported with relatively great rapidity toward various parts of the body.

All the animals used thus far were killed and autopsied at the end of the period of observation. Those which showed no signs of extension as indicated in the tables were found to be free from gross tuberculosis. The others invariably showed an average moderate to extreme degree of generalized tuberculosis that usually involved practically all the viscera and lymphoid tissue of the body.

If the bacilli are removed so promptly from the point of inoculation, the question arises of how long a time is required for them to reach the axillary or inguinal lymph nodes, for these structures invariably become diseased after primary inoculations of the skin which they drain. The presence of bacilli in these lymph nodes can be demonstrated very readily by removing them and inoculating them in emulsified form into normal animals, which may then be observed for the development of tuberculosis. Accordingly, the experiment which follows was performed.

Normal							
		Days since H37 inoculation					
		8	15	22	29	36	43
Animal number	Time between inoculation and excision						
1	1 hour	0	+(sl)	++	+++	++	++
2	,,	0	0	0	0	0	0
3	,,	0	0	+?	+	+++	+++
4	,,	0	0	0	0	0	0
5	2 hours	0	0	+?	+	++	++
6	,,	0	0	0	0	0	0
7	,,	0	0	+	++	+++	+++
8	,,	0	0	0	0	0	0
9	3 ,,	0	0	+?	+(sl.)	++	++
10	,,	0	0	+	++	++	++
11	,,	0	0	0	+?	++	++
12	,,	0	0	0	0	0	0
13	4 ,,	Dead					
14	,,	+	Dead				
15	,,	0	0	?	+	++	+++
16	,,	+	++	+++	+++	++++	++++
17	5 ,,	+?	+?	+?	+?	+	+
18	,,	++	++++	++++	++++	++++	++++
19	not operated	0	++	++++	++++	++++	++++
20	5 hours	+++	++++	++++	++++	++++	++++
21	6 ,,	Dead					
22	,,	+	++	++	++	++	++
23	,,	++	++	++	+++	++++	++++
24	not operated	+?	+	+++	++++	++++	++++

TABLE 2. SHOWING RESULTS OF FREQUENT EXAMINATIONS OF THE ANIMALS AFTER EXCISION, WHICH WAS DONE AT INTERVALS OF FROM ONE TO SIX HOURS AFTER INOCULATION

2. REMOVAL AND INOCULATION OF REGIONAL LYMPH NODES OF INOCULATED ANIMALS

Technique: Twenty-four normal guinea pigs were inoculated with an emulsion of H37, similar to the emulsions previously used, in the skin of the left side at a point equidistant from the axilla and groin. At varying hourly and daily intervals two animals of the group were killed, shaved in the axillary and inguinal regions on the side of inoculation, and their skins sterilized with five per cent carbolic acid. With sterile instruments for each situation, the axillary and inguinal lymph nodes were exposed; with other sterile instruments for each, these were separately removed and each was emulsified by being ground in a little physiological salt solution in a sterile mortar. Each emulsion was then inoculated into a normal animal; so that from each killed animal two new normal animals were inoculated, one with the axillary and one with the inguinal lymph nodes. The lymph nodes were removed and inoculated up to the eighth day after infection. The recipient animals were observed for palpable signs of infection weekly for ten weeks and were then killed and examined.

Most of the animals which received the material of the lymph nodes removed twenty-four hours or longer after infection developed tuberculosis, which showed clearly that, after a day following inoculation, bacilli had reached either axillary or inguinal lymph nodes or both. All recipient animals, which developed lymph-node enlargement, subsequently showed visceral tuberculosis at autopsy. The data are presented in table 3. In this table the records of all four animals inoculated at a given time from the tissues of the two donors are grouped in a single column and the "plus" indicates that one or more of the four animals developed palpable lymph nodes after inoculation with the tissues from one or the other of the donors. The lymph nodes removed from one of the animals at two hours after inoculation set up disease in the recipient. Those removed at and subsequent to one day after inoculation nearly always set up disease when inoculated into recipients. The two-day lymph nodes caused no disease, but three of the four recipient animals inoculated with the material taken on that day died too early for tuberculosis to develop. The significant finding, as shown in the table, is that bacilli reached the regional lymph nodes in animals inoculated intracutaneously within twenty-four hours after inoculation, and had thus traversed a distance which measures usually five centimetres or more.

The unexpected rapidity with which bacilli were transported from the area of inoculation raised the question of whether an injection of cutaneous lymphatics occurred at the time of inoculation and whether the pressure from the syringe forced the emulsion into these small vessels.

Normal												
Days since tissue inoculation	Time between inoculation and excision of nodes											
	Hours							Days				
	1	2	3	4	6	8	10	1	2*	4	6	8
8	o	o	o	o	o	o	o	o	o	o	o	?
13	o	o	o	o	o	o	o	+	o	+	+	+
20	o	o	o	o	o	o	o	+	o	+	+	+
25	o	o	o	o	o	o	o	+	o	+	+	+
34	o	+	o	o	o	o	o	+	o	+	+	+
41	o	+	o	o	o	o	o	+	o	+	+	+
47	o	+	o	o	o	o	o	+	o	+	+	+
53	o	+	o	o	o	o	o	+	o	+	+	+
63	o	+	o	o	o	o	o	+	o	+	+	+
75	o	+	o	o	o	o	o	+	o	+	+	+
Autopsy	o	+	o	o	o	o	o	+	o	+	+	+

*3 Animals died early

TABLE 3. SHOWING RESULTS OF INOCULATION OF ANIMALS WITH LYMPH NODES REMOVED AT VARYING INTERVALS AFTER INTRACUTANEOUS INOCULATION OF ORIGINAL ANIMALS

Results of inoculation of axillary and groin nodes removed from animals which had had intracutaneous inoculations at given intervals prior to removal. Each column represents the results from inoculation of four guinea pigs, one from the axillary and one from the inguinal nodes of each of two animals used as donors at the given interval after inoculation. A "plus" therefore means that tuberculosis developed in any or in all four of the animals. It indicates that tuberculosis followed inoculation of tissues removed at the given interval. See text for further comment.

To test this possibility each of 15 guinea pigs was injected intracutaneously with 0.1 cc. of a water suspension of impalpable prussian blue, and at irregular hourly and daily intervals the injected areas with a zone of skin, approximately 3 x 6 cm., were excised and cleared by the method of Spalteholz. Upon examination it was found that *in about half of the animals lymphatic injection of greater or less degree occurred.* One of these injections filled the lymphatics as far as 20 mm. from the point of injection; in a few it extended 5 to 15 mm. from the injection point; but in the larger number of the half showing lymphatic injection the vessels were injected only to a distance of 3 or 4 mm. It is therefore likely that, of the animals which showed very early dissemination (one and two hours) some may have represented lymphatic injections. But *all* the infected animals in which excision was delayed more than three hours after inoculation developed tuberculosis. This would indicate that, within this time after inoculation, bacilli were removed from the site of inoculation in all animals,—in those in which no lymphatic inoculation occurred, as well as in those in which such inoculation may have occurred. All lymphatic injection with the blue no doubt occurred immediately upon injection, for no evidence of later filling of these vessels appeared. Indeed, after one day no lymphatics were injected, and the whole area, often for 10 or 15 mm. peripheral to the injection mass, showed a marked diffusion of the blue.

DISCUSSION

Tubercle bacilli are transported from the site of primary inoculation in a normal animal very soon after their introduction. The above experiments have shown that guinea pigs inoculated into the skin usually develop visceral tuberculosis *even though the area of inoculation is enucleated within three hours after the inoculation occurred, and always develop it if excision is not done until four hours after the inoculation.* Five out of 12 animals (table 2) in which excision occurred within the first three hours after inoculation failed to develop tuberculosis; the remaining 7 became tuberculous, as did all in which excision was performed more than three hours after inoculation. Removal and inoculation of regional axillary and inguinal lymph nodes from skin-inoculated animals showed that the bacilli usually reached these points by the end of twenty-four hours after their introduction several centimetres distant.

That some bacilli get beyond the site of inoculation early and are not removed by excision of the site of inoculation was shown by Bahrdt (2)

who excised tissue at various intervals after inoculation of the skin, and then gave his animals skin tests with tuberculin. He found that animals in which excision was done five days or later after inoculation showed a diminished tuberculin reaction, but he was unable in this way to wipe out the reaction completely. He also excised the regional nodes together with the sites of inoculation but found, by getting reactions to tuberculin, that all infection was not removed in this way; that is, that bacilli had been carried beyond regional lymph nodes and had set up tubercle.

The situation with tubercle-bacillus infection seems to resemble that with respect to early dissemination of the *Treponema pallidum;* and clinical experience with syphilis has shown that secondary and tertiary stages develop in about the same manner in persons in whom there has been excision of the chancre as in those in whom there has been no interference with the evolution of the chancre. Neisser (3) demonstrated a very early dissemination of treponema pallidum from the site of inoculation, when he found (occasionally) that his animals developed syphilis when the area of inoculation was excised as early as eight hours after the inoculation had occurred. He also demonstrated the microörganisms in the spleen, bone marrow, and lymph nodes before the appearance of the chancre. Pearce and Brown (4) have described generalized infection with treponema in the heart's blood within seven days of the inoculation.

CONCLUSIONS

1. Tubercle bacilli are disseminated rapidly from a point of inoculation in the skin of normal guinea pigs.

2. Migration of bacilli from the site of inoculation is often accomplished within the first hour after their introduction, and some bacilli have always migrated from the area by three hours after inoculation.

3. Bacilli always spread from a point in the skin of the side to the axillary and inguinal lymph nodes within twenty-four hours of their inoculation. This is a distance of about 5 cm.

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STUDIES ON TUBERCULOUS INFECTION[1]

XI. THE EARLY DISSEMINATION OF TUBERCLE BACILLI AFTER INTRACUTANEOUS INOCULATION OF IMMUNE GUINEA PIGS OF REINFECTION

HENRY STUART WILLIS

In the foregoing study x it was shown that in normal guinea pigs there occurs a very early and rapid dissemination of tubercle bacilli from the point of intracutaneous inoculation, for within a very few hours bacilli are transported relatively considerable distances from the site of inoculation (1). The present study continues this investigation of the rate of distribution of tubercle bacilli, and presents similar work done on *immune* guinea pigs at the same time, and with the same dosage and technique, as used on the normal animals referred to above.

For the sake of unity and clarity the plan of the experiment outlined in the preceding paper will be restated here, because inoculations of bacilli, excisions of areas of inoculation at given time intervals after inoculation, and examination of animals and tissues were done simultaneously on pairs from groups of immune and nonimmune animals.

The experiment consisted of two main parts:

1. The enucleation of sites of inoculation (skin), at varying intervals after the latter was performed, and the subsequent observation of these same animals for the appearance of tuberculosis. If the technique of removal of the sites of inoculation was good, a nonappearance of infection later would prove that within any specified time bacilli had not progressed beyond the site of inoculation, while a development of infection would show that bacilli had made this transit.

2. The excision of lymph nodes draining the sites of inoculation, at varying intervals after intracutaneous infection, and *the inoculation of nodes into normal guinea pigs*. If any of the latter developed tuberculosis it shows that they had received bacilli which had travelled from the sites of skin inoculation to the regional lymph nodes within the time between skin infection and lymph-node removal. On the other hand,

[1] From the Kenneth Dows Fund for the Study of Tuberculosis of the Medical Clinic of the Johns Hopkins Hospital and University.

absence of infection would prove that, up to the time of removal of the lymph nodes, the bacilli had not progressed this far from the site of inoculation.

The experiment afforded the opportunity to study the fate of bacilli at the site as well as at their dissemination. Certain of the excised tissues from each group were therefore preserved in Zenker's fluid and studied histologically; other specimens were emulsified and inoculated into animals, in order to ascertain whether there occurred any reduction in the number of bacilli (or any alteration in virulence) in the immune as opposed to the normal animals.

1. EXCISION OF AREAS OF INOCULATION

Technique: Forty guinea pigs were inoculated subcutaneously in the right groin, each with 0.5 cc. of a heavy suspension of R1 tubercle bacilli on September 19, 1922. Strain R1 is a tubercle bacillus known to initiate lesion but not progressive disease after subcutaneous inoculations of the dosage stated. Seven weeks later (November 13) these animals and 30 normal guinea pigs were inoculated intracutaneously on the left side with 0.1 cc. of an emulsion of H37. By this time the R1 animals had become allergic and immune, and will hereafter in this paper be referred to as immunes, while the others will be designated as non-immunes. At intervals of 1, 3, 6, 10 and 24 hours, and from 2 up to 56 days after the H37 inoculation, animals of the groups of immunes and nonimmunes were treated in pairs as follows: With the animal under ether, the site of inoculation was washed with 70 per cent alcohol and an alcohol sponge was held on the area for one minute, when the alcohol was washed off with sterile water. The area, including a zone of surrounding tissue measuring 15 to 18 mm. in diameter, was cleanly enucleated and the excised area covered with celloidin. Anesthesia continued in each animal about two minutes. The possibilities of error in this technique are discussed in the preceding paper (1).

After excision each animal was examined frequently for enlargement of the axillary and inguinal lymph nodes on the side of the inoculation, which would be evidence of extension of the infection to these parts. Moreover frequent observation would also disclose how long after excision such extension developed and thus indicate the relative numbers of bacilli which had cleared the field of inoculation before operation.

Marked differences appeared very early in the two groups. In the

normals, as has been shown in the foregoing paper, extension to the regional lymph nodes developed very early and was progressive. On the other hand, the immune animals at first showed no signs whatever of enlargement of the lymph nodes. When they did develop, the signs were slight, the lymph nodes being very little enlarged; and they occurred first in the "unoperated" animals, and enlargement, while usually progressive, was very slow. Ultimately, enlargement took place in the immunes in which excision had taken place at seven days and later after inoculation. But *no enlargement ever developed in any in which excision occurred before the seventh day after inoculation.* Comparisons of the rate of dissemination, and some of the data concerning the extension of infection to regional lymph nodes, are given in table 1, in which are listed alternate animals of the immune and nonimmune groups.

Analysis of table 1: One should note first the animals of each group that are listed toward the bottom of the table. In these animals no excision was made until quite late, and they may be looked upon, therefore, up to the date of operation, as controls to show what happened in "unoperated" animals in the earlier days after inoculation. It will be seen that in the "unoperated" animals of the immune group moderate enlargement of the lymph nodes, as indicated by a plus sign, had developed by the twenty-second to the twenty-fifth day after inoculation and that, in general, anatomic changes in the regional lymph nodes in these animals were either stationary or very slowly progressive. In the nonimmune group, on the other hand, those animals, before operation, would show uniform enlargement by the tenth day after inoculation and the process was rapidly progressive.

A: Immune animals: Even a cursory glance at the table will reveal a marked difference in the two groups, and closer examination will show that soon after the skin inoculations there took place remarkably little spread in the immunes as compared with the nonimmunes. The immune animals may be divided into two lots: (1) those in which excision of the sites of inoculation occurred before the seventh day after inoculation; and (2) those in which excision occurred at seven days or later after inoculation. *Of those in which excision occurred within the first seven days none developed any signs of spread of the infection to the regional lymph nodes and none showed tuberculosis at autopsy.* Of the remaining animals about one-half developed enlargement of the lymph nodes and slight visceral tuberculosis, but it was not until eighteen days after

Immune	Non-immune	Time between inoculation and excision	Days since Hs7 inoculation														Autopsy	
			7	10	14	18	22	25	30	35	40	55	64	80	94	101	Nodes	Viscera
1		1 hour	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
3		3 hours	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
5		6 „	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
7		10 „	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
9		24 „	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
11		2 days	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
13		4 „	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
15		7 „	o	o	o	o	o	o	o	o	o	?	++	+++	+++	+++	+	+
17		10 „	o	o	o	o	o	o	o	o	o	+	+	+	?	?	o	o
23		14 „	o	o	o	o	o	o	o	+	+	+					+	o
25		18 „	o	o	o	o	?	+	+	++	++	++					+	+
26		22 „	o	o	o	o	o	+	+	+	+	+					+	o
27		25 „	o	o	?	?	+	+	+	+	++	++					o	o
28		30 „	o	o	o	o	+	+	+	+	+	+					o	+
29		56 „	o	o	?	+?	++	++	++	++	++	+++					+	+
	31	1 hour	o	o	+	+	++	+++	+++	+++	+++	+++					+	+
	33	3 hours	o	o	o	o	o	o	o	o	o	o					o	o
	35	6 „	o	o	o	o	o	++	++	++	++	++					+	+
	37	10 „	o	o	+	++	++	++	++	+++	+++	+++					+	+
	39	24 „	o	o	+	+	+	+	+	+	++	++					+	+
	41	2 days	o	?	?	+	++	++	++	++	++	++					+	+
	43	4 „	o	o	++	++	++	++	++	++	++	++					+	+
	45	7 „	o	+	+	+++	+++	+++	++++	++++	++++	++++					+	+
	47	10 „	o	+	++	++	+++	+++	+++	+++	+++	+++					+	+
	53	14 „	o	+	+	++	+++	+++	+++	+++	++++	++++					+	+
	55	18 „	o	+	++	++	++++	++++	++++	++++	++++	++++					+	+
	56	22 „	o	+	+	+	++	++	++	+++	+++	++++					+	+
	57	25 „	o	+	++	++	++	++	++	++	++	+++					+	+
	58	30 „	o	+	++	+++	++++	++++	++++	++++	++++	++++					+	+
	59	56 „	o	+	++	++++	++++	++++	++++	++++	++++	++++					+	+

TABLE 1. COMPARISON OF THE RESULTS OF EXCISION OF AREAS OF INOCULATION AND OF AUTOPSY FINDINGS AFTER INFECTION OF NORMAL AND IMMUNE GUINEA PIGS

Results of examination of the axillary and inguinal lymph nodes on the side of intracutaneous inoculations, at intervals of from 7 to 101 days after inoculation of immune and nonimmune animals, in which excision of the area of inoculation was performed from one hour to fifty-six days after inoculation. The excisions were done simultaneously on animals from each group. Only every alternate, instead of every animal, is charted because of lack of space. The dotted lines represent graphically the time of excision in relation to the time of observation of the animal. (For further description see the text.)

inoculation that the first enlargement of the lymph nodes appeared, and this was not definite. Twenty-two days were required for bacilli introduced into the skin to reach either the axillary or inguinal lymph nodes, and set up sufficient changes for the nodes to become palpable, and even after palpable lesion was established, progression of the process was very slow. The lymph nodes never became as large as those in the nonimmune animals. Indeed, in several of the animals palpable changes developed, continued for a few days, and then subsided. This circumstance suggested that possibly, since all tissues of infected, hypersensitive animals are allergic, the local immune reaction of the tissues (lymph nodes) had destroyed those bacilli which arrived at new situations on their route centralward, and all of them if they were in sufficiently small numbers.

B: Nonimmune animals: In the nonimmune animals the spread of infection was rapid and progressive. This portion of the table is discussed in the foregoing study (1).

Autopsy results in the two groups: The differences in these two groups at autopsy were quite as striking as those which the animals showed before death. Of the 40 *immunes*, 18 at one time or another presented enlarged nodes in either the groin or axilla, but only 9 of the whole group showed visceral tuberculosis (spleen, liver, lungs, tracheobronchial nodes) and in these there was usually a single focus or, at most, a few small foci of 1 or 2 mm. diameter. None of the animals in which excision of site of inoculation was performed earlier than seven days after inoculation showed tuberculosis. On the other hand, only two animals in the group of 30 *nonimmunes* escaped generalized infection, the others showing at autopsy an average moderate degree of tuberculosis with enlarged and diseased spleen; with lungs containing from one or two suspiciously tuberculous areas to as many as forty sago-like tuberculous bodies from 0.5 to 5 mm. in diameter and in varying degrees of caseation; with tracheobronchial lymph nodes sometimes enlarged to enormous proportions, with or without caseation; and frequently with involvement of the liver. In some of the nonimmunes one or another viscus was free from visible tubercle, but in none (except nos. 32 and 34) were all viscera free from disease. The presence or absence of disease at autopsy is indicated in table 1.

If dissemination appears not to occur as promptly in immunes as it does in nonimmunes, the question of what happens to the bacill at the point of inoculation becomes an important one, and answer to this

question was sought in the following way: At operation the excised tissue of one animal from each group was emulsified and inoculated into normal guinea pigs, to learn something as to the relative numbers (or virulence?) of the bacilli contained in the excised tissue. The tissue from the second animal of each group was devoted to histological study. The results of each procedure are given below.

Results of tissue inoculations: As stated above, the original H37 animals, in both the immune and nonimmune groups, were operated upon at various times after H37 inoculation; that is, some of the animals carried the areas of inoculation a very short time, and others a relatively long time before excision was performed. Excised tissues which had held H37 bacilli varying lengths of time were, at the time of excision, inoculated into animals, to determine whether fewer bacilli were contained in the tissues from immunes than in those from nonimmunes. The animals which received these inoculations invariably developed tuberculosis, whether they had been inoculated with tissue from immune or nonimmune animals. In most of the instances of early excision the differences were equivocal, and the indication was that approximately equal numbers of bacilli were present in the tissues excised from each group of animals. In several cases the tissues excised two weeks and later after inoculation set up, in recipient animals, disease which showed wider differences for the two groups. Somewhat more extensive lesion developed from the inoculations of tissue from the nonimmunes, as though more bacilli were present in the tissue from nonimmunes than from immunes. These differences, however, were by no means marked or striking. Whether some bacilli may have undergone bacteriolysis and destruction in the immunes, one cannot say; this will be discussed below.

Microscopic examination of excised tissue: When one area of inoculation was removed and used for further inoculation, one removed area was used for microscopic examination. Sections of this tissue were stained for tubercle bacilli and histological study. In the immune tissue, at ten hours after inoculation, bacilli were present in abundance, many of them in loose collections in or about polymorphonuclear leucocytes. There were numerous small islands of these cells. At twenty-four hours still further signs of acute inflammation were present with many polymorphonuclears, much exudation and some distortion of the layers of the skin. By the seventh to the tenth day the infiltration consisted largely of lymphocytes. By the end of the second week many

patches of round-cell infiltration appeared and were surrounded by normal tissue. After the second week bacilli were much less numerous than in the nonimmunes, and appeared rather in the clumped arrangement described by Rist and Rolland (5) and attributed by them to bacteriolytic influence. In the nonimmunes the histological reaction was of slower development up to ten days when one could find a fairly dense infiltration by lymphocytes with a good sprinkling of polymorphonuclear leucocytes. Bacilli were much more abundant than in the tissues of the immunes and were intracellular and extracellular in about equal numbers. Examinations of tissues taken from both groups later showed caseation, which was more marked in the nonimmunes. In short, the reaction in the immunes was prompt, abundant and of comparatively short duration; in the nonimmunes it was slow in developing and presented no features of an acute inflammation.

2. REMOVAL AND INOCULATION OF REGIONAL LYMPH NODES OF IMMUNE ANIMALS

Technique: It was pointed out in the preceding paper that bacilli traverse the distance between the point of inoculation and the regional nodes in animals of first infection in a surprisingly short time. At the time this part of that study was made, a similar study was made on immune animals. Thirty-eight immune animals were inoculated with H37, together with the 24 normals already recorded (1). With the same technical procedure the axillary and inguinal lymph nodes were removed, severally and aseptically, from given animals at given intervals of from one hour to nine weeks following inoculation, and were inoculated into normal animals which were then observed at weekly intervals for signs of tuberculosis. The results are presented in table 2.

Analysis of table 2. The results showed an entire absence of tuberculosis in all animals inoculated with lymph nodes removed from the immunes up to and including two weeks after inoculation of the latter. In those animals that had received inoculations of tissue, at three weeks after infection of the donor and regularly thereafter, the presence of H37 bacilli was demonstrated. The plus sign represents the findings of enlargement of lymph nodes in recipient animals after the inoculation of emulsions of axillary or inguinal lymph nodes from immune animals. When compared with table 3 of the foregoing study X this table is significant in that the metastasis of bacilli to the regional lymph nodes

in the immune animals was not found to occur within two weeks after intracutaneous inoculation, while in normal animals it took place within one day after inoculation.

Allergic																		
Days since tissue inoculation	Time between inoculation and excision of nodes																	
	Hours							Days					Weeks					
	1	2	3	4	6	8	10	1	2	4	6	8	2	3	4	5	6	7	9
8	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	+
13	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+	+	+	+
20	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+	+	+	+
25	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+	+	+	+
34	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+	+	+	
41	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+	+	+	
47	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+	+		
53	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+			
63	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+				
75	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+				
Autopsy	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	+	+	+	+

TABLE 2. RESULTS OF INOCULATION OF ANIMALS WITH LYMPH NODES REMOVED FROM IMMUNE ANIMALS AT VARYING INTERVALS AFTER INTRACUTANEOUS REINFECTION

Results of inoculation of axillary and inguinal lymph nodes removed from immune animals which had had intracutaneous inoculations at given intervals prior to excision. Each column represents the results from the inoculation of four guinea pigs, one with each axillary and one with each inguinal lymph node of two reinfected guinea pigs. (See text for comment.)

DISCUSSION

Marked differences appear between dissemination of tubercle bacilli in immune guinea pigs and that in normal guinea pigs. Bacilli are removed from the site of inoculation soon after infection in animals of first infection (nonimmunes), and if the inoculation area is allowed to remain unexcised for more than three hours the animal invariably develops tuberculosis. But this is altogether unlike the series of events following inoculation and excision in immune animals of reinfection; for in these animals early extension is decidedly the unusual thing, although it can occur (for a certain small number developed tuberculosis).

It has been suggested that the distribution of bacilli through the body, and the promptness with which the distribution occurs after inoculation, may be very important factors in the immunity or lack of immunity of a given animal body to the disease, and that the hypersensitive state of previously infected animals may confer immunity to reinfection, in part, by *the allergic inflammation which mechanically limits the spread of bacilli* from the site of inoculation. This idea has been developed particularly by Krause (2), who in 1917 and earlier, directed attention to the probable significance of the acute inflammatory, allergic reaction which is thrown up as a barrier about new bacilli and facilitates fixation of bacilli at the site. With Peters (3), in 1920, the same writer, emphasizing the fact that, when an allergic animal is reinfected with tubercle bacilli, an acute inflammation develops at the site of reinfection within a few hours, and that such animals develop relatively scant visceral tuberculosis from the reinfection of virulent bacilli, remarked that "no one . . . . . can help being impressed by the probability that this initial inflammation plays a large part in the turn of subsequent events—in the immunity which later developments show as having existed." In several later communications Krause (4) (5) again explained his conceptions of the mechanics of the inflammatory wall, which so rapidly forms about reinfecting bacilli, in arresting the spread of the latter.[2]

Such observations have made desirable the direct scientific solution of several questions as to possible relationships between the allergic reaction, bacillary dissemination and immunity to tuberculosis. Is the spread of bacilli mechanically limited at the site of inoculation and is it thus that the immunity is conferred? Do bacilli pass the barrier of inflammation and spread to the tissues? If so, are they disseminated throughout the immune animal more slowly than in the normal nonimmune, and is this slower metastasis a factor of immunity? Does the local allergic reaction at the point of second and later focalization aid in the protection? Does a bacteriolysis occur at the site of inoculation with the result that fewer bacilli reach the animal tissues? Is some change produced in the virulence of the bacilli after their inoculation into sensitive tissues?

No doubt, some of the bacilli inoculated into immune animals are transported from the site of inoculation before the barrier of inflamma-

[2] See Krause, A. K., *Human Resistance to Tuberculosis at Various Ages of Life, Appendix A*, AMERICAN REVIEW OF TUBERCULOSIS, 1925, xi, 303.

tion develops, and no doubt also, what happens subsequently to such bacilli is important. Wherever they settle in the immune animal, they lodge in allergic tissue and must, it seems, excite a local inflammatory, allergic reaction, however slight. Accordingly, a bacillus, or a few bacilli, which had been carried from the point of inoculation to the regional axillary or inguinal lymph nodes, would be met with a new barrier of inflammation which would tend to limit any further progress centripetally. Normally, a lymph node offers resistance to particulate matter and arrests much that comes its way, and it is reasonable to suppose that it would hold bacilli long enough for the local allergic reaction to develop in many cases.

Rist and Rolland (6) have, by histological examination, demonstrated that bacteriolysis appears to occur at the site of intracutaneous inoculation in immune guinea pigs, for they showed fragmented, disintegrating bacilli in agglutinated clumps in histological sections of intracutaneous foci.[3] There does not appear, however, to be any definitely conclusive evidence that the virulence of tubercle bacilli has been altered by residence in animals, although much study of this problem has been recorded. Bacilli recovered from allergic animals initiate typical lesions and disease when inoculated into other animals, and, although Thiele and Embleton (7) claimed to be able to vary the virulence at will, their work has failed of confirmation in competent hands. It seems entirely *improbable* that the immune animal produces an attenuation rather than death of bacilli, because when H37 bacilli are recovered from immune animals and inoculated into other animals, typical, progressive H37 disease ensues.

CONCLUSIONS

1. In marked contrast to the rapid dissemination of tubercle bacilli from a point of inoculation in the skin of *normal* guinea pigs of first infection, dissemination of bacilli is materially retarded in the skin of guinea pigs of reinfection, made allergic or immune by a previous infection with tubercle bacilli.

2. In the normal animal transit from the site of inoculation in the skin to the axillary or inguinal lymph nodes, 4 or 5 cm. distant, requires twenty-four hours or less. In the immune animal such transit is ac-

[3] See also remarks by Krause on the lysis of tubercle bacilli in *Environment and Resistance in Tuberculosis*, Williams & Wilkins, Baltimore, 1923, and *Human Resistance to Tubeculosis at Various Ages of Life, Appendix A*, AMERICAN REVIEW OF TUBERCULOSIS, 1925, xi, 303.

complished in a little less than three weeks; longer than two weeks is always required.

3. In the immune animal, a few of the bacilli introduced into the skin do ultimately reach remote parts of the body, but their numbers are relatively small, compared with the numbers that spread from the site of reinfection in the normal animal.

4. The immune animal, therefore, appears definitely to fix bacilli at the point of introduction, for at least longer than four days after inoculation, and to prevent widespread or early dissemination. This finding is a further confirmation of the hypothesis that specific immunity to tuberculosis is accomplished in part through a fixation of bacilli of reinfection by the rapid inflammatory response of the allergic reaction.

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ON THE PRODUCTION OF ACID-FASTNESS IN NON-ACID-FAST BACILLI[1] [2]

LEO KEMPF CAMPBELL

In view of the fact that the work of Bienstock (1) and Gottstein (2), who reported acid-fast characteristics for non-acid-fast bacilli which were cultivated on media containing a lipoidal substance, has continued to appear in textbooks, it was suggested that this work be repeated. No confirmation of their results could be found in the literature.

TECHNIQUE

The medium employed was glycerol-broth-agar in amounts of 5 cc., to which 1 cc. of the lipoidal substance was added. The tube was thoroughly shaken just before the agar solidified so as to obtain a uniform suspension. The lipoidal substances used were butter, lanolin and beeswax.

The media containing the above lipoidal substances were inoculated with *B. prodigiosus*, *B. typhosus*, *B. proteus*, and *B. mucosus capsulatus*. The microörganisms were transferred every 48 hours for a period of sixteen weeks.

Two acid-fast stains were made on bacilli from each tube by the following methods: The microörganisms were allowed to dry on the slide in the air. One slide was washed three times with ether, stained by the Ziehl-Neelsen technique, and decolorized for two minutes; the other was not washed with ether but was stained directly.

RESULTS

After sixteen weeks of cultivation on lipoidal media the non-acid-fast bacilli used had not been rendered acid-fast. In many instances isolated bacilli, or even clumps, were found to stain by the Ziehl-Neelsen method, if the slide had not previously been washed in ether. The microorganism which took the stain appeared to have a fatty capsule and

[1] From the Department of Pathology of the University of Chicago and the Otho S. A. Sprague Memorial Institute.

[2] Work done under a grant to Esmond R. Long from the National Tuberculosis Association.

was not stained solid as is a tubercle bacillus. In the slides examined, which were washed twice with ether, no acid-fast bacilli were found.

As a means of check on the method used, *B. tuberculosis* and *B. leprae* were air-dried on a slide which was then washed with ether. The acid-fast characteristics were not removed.

CONCLUSIONS

The results of Bienstock and Gottstein could not be confirmed. The non-acid-fast bacilli used in this investigation were not rendered acid-fast by prolonged cultivation on solid media containing a lipoidal substance in suspension. The results obtained by Bienstock and Gottstein were probably due to occluded lipoids, which in the above investigation were removed by washing with ether.

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STUDIES ON THE AMINO-ACID CONTENT OF THE TUBERCLE BACILLUS[1, 2]

LEO KEMPF CAMPBELL

An analysis for the amino-acid content of the protein of the tubercle bacillus has been reported by two groups of investigators in recent years. Tamura (1), using the process of Kossel and Kutscher (2) as modified by Weiss (7), and Johnson and Brown (3), using the VanSlyke method, have complete analyses as far as the methods employed would permit. Accurate colorimetric methods for the estimation of histidine (5) and tyrosine (6) have more recently been developed by Hanke and Koessler. It was hoped that an exact analysis of this protein for its amino-acid content and nitrogen distribution might ultimately shed some light on its immunological characteristics.

EXPERIMENTAL PART

Defatting process: Four hundred and fifty grams of tubercle bacilli[3] were dried in a vacuum desiccator over H_2SO_4 for two weeks. They were then treated with 80, 90, and 95 per cent, and cold absolute alcohol for twenty-four hours each, followed by forty-eight hours of refluxing with hot absolute alcohol. The bacilli were leached for four days with 1500 to 2000 cc. of toluol, the solvent being changed every day. They were then refluxed with medium boiling petroleum ether for one day and filtered on paper while hot. The fat-free bacilli were allowed to stand at room temperature for two days, and the last traces of the petroleum ether were removed by heating to 70 to 80° for thirty minutes in an electric oven. Two hundred and seventy grams of the dry, fat-free bacilli, an almost white powder, were thus obtained for the analyses given below. A Kjeldahl determination on these microörganisms showed them to contain 10.62 per cent nitrogen.

[1] From the Department of Pathology of the University of Chicago and the Otho S. A. Sprague Memorial Institute.

[2] Work done under a grant to Esmond R. Long by the National Tuberculosis Association.

[3] These bacilli were obtained from Dr. Marion Dorset of the U. S. Department of Agriculture, Washington, D. C., and were of the bovine type, cultivated on broth.

Estimation of histidine, arginine and lysine: The method employed in the estimation of histidine, lysine, and arginine is one in which each amino acid can be determined by a direct method. The dibasic acids are precipitated by phosphotungstic acid by the regular process and the histidine is estimated colorimetrically. The arginine and histidine are separated from lysine by the alkaline silver process and the arginine is determined directly by the method of VanSlyke (4). The lysine is determined by obtaining the total nitrogen on the filtrate from the alkaline silver precipitate.

Two samples, each 5.5 grams, of the fat-free bacilli were hydrolyzed for 48 hours with 200 cc. of 20 per cent hydrochloric acid. The hydrolysate did not give a biuret reaction.

Estimation of histidine: The method employed was that of Hanke and Koessler (8) in which the hydrolysate is freed from HCl, volatile phenols, ammonia and humin, and the dibasic amino acids precipitated as the phosphotungstates. The phosphotungstates are dissolved in alkali, diluted to exactly 1000 cc. and the histidine estimated directly in this liquid by a colorimetric process. Of this liquid,

0.1 cc. gave a color (5) equivalent to 5 mm. (CR−MO)
0.2 cc. gave a color (5) equivalent to 10 mm. (CR−MO)
0.3 cc. gave a color (5) equivalent to 15 mm. (CR−MO)

Both samples gave identical readings and the colors matched perfectly. By referring to the table of Koessler and Hanke (5) the above samples of fat-free tubercle bacilli were found to contain 1.35 per cent of histidine calculated as the free base. Hence, 3.41 per cent of the total nitrogen of the fat-free bacilli was accounted for as histidine.

Separation of histidine and arginine from lysine: The remainder of the above solution was freed from phosphotungstic acid by means of $BaCl_2$ and NaOH. The barium was removed exactly with H_2SO_4. The liquid was treated with sufficient $AgNO_3$ to remove the chloride ion. The filtrate from the AgCl was then subjected to a silver precipitation with $AgNO_3$ and baryta in excess (2). This divides the material into two fractions, namely, a silver precipitate which contains histidine and arginine and a silver filtrate which should contain only lysine.

Estimation of arginine: The silver precipitate was decomposed by digesting with HCl for 5 hours, and the excess hydrochloric acid removed in a vacuum at 60°. The residue was dissolved in water and made up to exactly 500 cc. In order that the histidine and arginine results could be

checked, the total nitrogen content of this fraction was determined, as follows:

	grams
Total N_2 of sample no. I	0.175
Total N_2 of sample no. II	0.178

Another portion of the above solution was then subjected to the alkaline distillation process of Osborne, incorporated in the method of VanSlyke (4) for the estimation of arginine. The values obtained were as follows:

	grams
I. Total N_2 as arginine	0.160
II. Total N_2 as arginine	0.165

The fat-free tubercle bacilli were thus shown to contain 9.2 per cent of arginine, and 27.87 per cent of the total nitrogen was accounted for as arginine.

That the silver precipitate contained nothing but arginine and histidine is proved by the following figures:

Sample I		*Sample II*	
Total N_2 as arginine	0.160	Total N_2 as arginine	0.165
Total N_2 as histidine	0.020	Total N_2 as histidine	0.020
Total N_2 calculated	0.180	Total N_2 calculated	0.185
Total N_2 found	0.175	Total N_2 found	0.178

Estimation of lysine: The filtrate from the insoluble silver compounds of arginine and histidine contains lysine. This liquid was freed from traces of silver by adding HCl, and from barium by the addition of H_2SO_4. The solution was then concentrated, diluted to exactly 200 cc., and the total nitrogen content determined.

	grams
I. Total N_2 as lysine	0.010
II. Total N_2 as lysine	0.010

Using the above results, the lysine content of fat-free tubercle bacilli was found to be 0.95 per cent, and 1.71 per cent of the total nitrogen was accounted for as lysine.

Estimation of glutamic acid: The method employed in this determination was essentially that of Hlasiwetz and Habermann (9). Two hundred and sixteen grams of fat-free bovine tubercle bacilli were hydrolyzed for 42 hours with 2500 cc. of 20 per cent hydrochloric acid.

The solution so obtained did not give a biuret reaction. The hydrolysate was filtered through a Buchner funnel, and the material on the funnel washed with hot water until the washings were colorless. The filtrate was concentrated *in vacuo* at 56° to a volume of 200 cc. This solution was transferred to an ice-bath and saturated with gaseous HCl. It was inoculated with a crystal of glutamic acid hydrochloride and placed in a refrigerator for two weeks to permit complete precipitation. At the end of this time the flask was placed in a freezing mixture for three hours and the crystals filtered through canvas on a Buchner funnel. The crystals, freed as far as possible from the mother liquor by suction, were washed with a few cubic centimetres of ice-cold alcoholic HCl. The contents of the funnel were transferred quantitatively to a flask and dissolved in 100 cc. of water. At this time the precipitation process was repeated, but the flask was allowed to remain in the refrigerator for only three days, placed in the freezing mixture, and the crystals filtered and washed as above. The crystalline precipitate was dissolved in 300 cc. of water and decolorized with animal charcoal. The solution, which was now amber colored, was made alkaline with barium hydroxide, heated on the water-bath, and finally boiled for thirty minutes to permit of complete removal of the ammonia. The barium was removed exactly with sulphuric acid, and the barium sulphate filtered off and washed thoroughly with hot water. This aqueous solution was then evaporated on the steam-bath until crystals began to separate out. The mixture was transferred to a refrigerator, where it was allowed to crystallize for 24 hours. The crystals were separated by filtration on a Hirsch funnel, and washed with a little ice-cold concentrated hydrochloric acid. The mother liquor was concentrated and a second and third crop of crystals obtained.

By using this method, 9.2 gm. of glutamic acid hydrochloride having a melting point of 198° (recorded 198°) were isolated. This is equivalent to 7.37 gm. of the free base, 3.4 per cent of the fat-free microörganisms. Therefore, 3.05 per cent of the total nitrogen was accounted for as glutamic acid.

Estimation of tyrosine: Tyrosine was estimated by a process that has recently been devised by Dr. M. T. Hanke (6), but which has not yet been published. It consists essentially in hydrolyzing the protein with H_2SO_4, removing histidine in alkaline solution with Ag_2SO_4, and converting the tyrosine quantitatively into a mercury derivative, with the Hg bound to C in the benzene ring. From this insoluble complex, tyrosine

can be regenerated by heating with HCl. The solution finally obtained contains only traces of substances other than tyrosine; hence the tyrosine can be estimated colorimetrically by the process previously described by

TABLE 1

Distribution of nitrogen in protein of the tubercle bacillus

	TAMURA (1)	JOHNSON AND BROWN (3)	CAMPBELL
	per cent	*per cent*	*per cent*
Total nitrogen	100.00	100.00	100.00
Total hexone base nitrogen	10.66	25.80	32.99
Histidine nitrogen	1.53	11.48	3.41
Arginine nitrogen	7.64	10.63	27.87
Lysine nitrogen	1.49	3.69	1.71
Glutamic acid nitrogen			3.05
Tyrosine nitrogen	Present		0.73
Tryptophane		Present	Present
Melanine nitrogen	15.79	4.11	9.13
Cystine nitrogen		1.26	1.26
Non-amino nitrogen	7.47	9.34	9.34
Nitrogen accounted for	33.92	40.51	56.50

TABLE 2

Composition of the protein of the tubercle bacillus

Calculated from column 3, table 1

	CAMPBELL
	per cent
Histidine	1.35
Arginine	9.20
Lysine	0.95
Glutamic acid	3.40
Tyrosine	0.96
Tryptophane	Present

Hanke and Koessler (10). The tyrosine solution finally obtained was diluted to 500 cc., of which

I. 0.1 cc. gave a color equivalent to 4.8 mm. (F−MO)
0.2 cc. gave a color equivalent to 9.6 mm (F−MO)

II. 0.1 cc. gave a color equivalent to 4.6 mm. (F−MO)
0.2 cc. gave a color equivalent to 9.1 mm. (F−MO)

By referring to the table compiled by Hanke and Koessler (10) it was found that sample I contained 0.03 gm. and sample II 0.0285 gm. of tyrosine. Therefore, the fat-free tubercle bacilli contain 0.96 per cent

of tyrosine, and 0.73 per cent of the total nitrogen is accounted for as tyrosine.

Estimation of melanine nitrogen: A total nitrogen determination by the Kjeldahl method was made on the entire melanine fraction from the histidine analysis. The fat-free tubercle bacilli were found to contain 9.13 per cent of the total nitrogen in the melanine fraction.

Detection of tryptophane: Color tests of moderate strength for tryptophane were obtained on the fat-free microörganisms.

The results obtained by the procedures described above may be summarized in tabular form (tables 1 and 2). For convenience the figures of Tamura (1) and Johnson and Brown (3) are cited in parallel columns for comparison. If the figures obtained by Johnson and Brown for cystine and non-amino nitrogen are added to the findings recorded above, a total of 56.5 per cent is thus accounted for.

SUMMARY

As noted in the table the nitrogen as hexone bases was found to be 32.99 per cent of the total. This agrees fairly well with the figure of Johnson and Brown (3) as regards the total amount. However, in my investigation a much larger amount of arginine and a smaller quantity of histidine were found than was noted in their report. The figures obtained for the hexone bases in the investigation were as follows: Arginine nitrogen 27.87 per cent, histidine nitrogen 3.41 per cent, and lysine nitrogen 1.71 per cent. Quantitative determinations on tyrosine and glutamic acid in tubercle bacilli were made for the first time. Glutamic acid nitrogen represented 3.05 per cent and tyrosine nitrogen 0.73 per cent of the total nitrogen of the fat-free bacilli.

From the results summarized above it may be concluded that the protein of the tubercle bacillus is in some respects similar to the histones, all of which contain large quantities of arginine.

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THE ALANINE AND HISTIDINE METABOLISM OF THE TUBERCLE BACILLUS[1,2]

LEO KEMPF CAMPBELL

Bouveault (1) was the first to make a detailed study of the nitrogen utilization of the tubercle bacillus. He used glycerol-broth, and studied the consumption of ammonia and amino nitrogen during growth. He found that creatine and creatinine were readily used as sources of nitrogen.

The first attempt to cultivate tubercle bacilli on synthetic media was by W. Kühne (2), who found that a luxuriant growth could be obtained on a medium composed of leucine, asparagine, taurine, ammonium mucinate, glycerol, sodium chloride and the ash of beef extract.

Proskauer and Beck (3) shortly afterward, using Kühne's formula, determined its growth-promoting constituents. They also carried their observation on to other amino acids. They found that glycine was suitable as the sole source of nitrogen, but if substituted glycines are used, such as sarcosine, $CH_2CHNCH_3 \cdot COOH$, and trimethyl glycine or betaine, growth did not take place. Glycine combined with benzoic acid, as in hippuric acid, did not support growth. After using many nitrogenous substances these authors concluded that ammonia and the simpler amino acids and acid amides were utilizable as the sole source of nitrogen. Substituted amino, imino, nitrate, and nitrite nitrogen, as well as nitrogen in complex organic combination, such as purines and aromatic amino acids, was unsuitable for utilization by the tubercle bacillus.

Tiffeneau and Marie (4), using Proskauer and Beck's formula with ammonium sulphate as the sole source of nitrogen, found after eight weeks of growth that two-thirds of the ammonia had been removed from the media to be incorporated in the bodies of 4 gm. of dry organisms.

Kendall, Day and Walker (5), using a rapidly growing tubercle bacillus of practically no virulence and peptone-glycerol-broth, found

[1] From the Department of Pathology of the University of Chicago and the Otho S. A. Sprague Memorial Institute.

[2] Work done under a grant to Esmond R. Long by the National Tuberculosis Association.

that the ammonia accumulated rapidly at first, and then receded. The cause of this recession was not determined. When asparagine was used as a sole source of nitrogen a parallelism was observed between the weight of the bacterial pellicle and the ammonia content of the broth. These investigators also found that with ammonium nitrogen as the sole source a peak of 10 per cent withdrawal was reached in fourteen days.

Long (6), using the same strain of tubercle bacillus that was used by the author, studied the liberation of ammonia from glycine, acetamide and asparagine. Ammonia was found to be liberated by the growth of the bacillus in all cases, but more rapidly from the amino group of glycine than the amide group of acetamide. In asparagine, which contains both amino and amide groups, the amide group was more readily attacked.

Long also followed the nitrogen utilization in the same strain of microorganisms in glycerol-peptone-broth. He found a great decrease in imino nitrogen and a relatively constant concentration of amino nitrogen. This he explained on the basis of the peptone acting as a storehouse for amino acids while the imino nitrogen was withdrawn. Long also found that a pepsin digest supported a much more abundant growth than did a trypsin digest.

Rettger (7) and his associates found that amino-acid-free peptone was not directly available for bacterial nutrition, being utilized only when sufficient more readily assimilable nitrogen was present to construct the enzyme machinery for attacking the larger molecules.

Burrowes and Neyman (8) found that amino acids, although available for direct anabolism by most cells, were nevertheless directly toxic for embryonic tissues in even a relatively low concentration.

Masucci (9) found that much larger yields of tubercle bacilli were obtained if amino acids were added to the broth medium.

Armand-Delille, Mayer, Schaeffer and Terroine (10), using a medium containing arginine and glycine reported rapid utilization of these two amino acids by the tubercle bacillus. In a later report (11) they concluded that two sources of nitrogen are necessary, both amino and imino. This observation was made on media prepared from many amino and imino compounds.

Long (12), considering as established facts the usefulness of amino acids and their deaminization metabolism, has attempted to learn the method by which ammonia is liberated from them, believing that the

liberation of the latter, on the one hand, and an organic acid, on the other, may account for the well-known reaction changes of the culture medium. He grew the tubercle bacillus first on an alanine-glycerol medium and then replaced the alanine in a series of experiments by ammonium pyruvate, propionate and lactate, and ethylamine. Growth occurred with ammonium lactate or pyruvate, but ammonium propionate and ethylamine did not support growth.

Long later tested growth on a number of other amino acids and nitrogenous compounds. The amino acids containing the benzene ring, tyrosine, phenyl alanine, and tryptophane were not suitable for the sole source of nitrogen. Leucine and histidine were utilized rapidly. Long believes that the substance remaining, after the amino group is removed from the aromatic amino acids, is inhibitory to growth. Propionamide was as well used as alanine. Creatinine, which contains imino but not amino nitrogen, did not support growth, a different result from that obtained by Bouveault and his collaborators. Urea was likewise unutilizable.

Hanke and Koessler (13), using the same strain of tubercle bacillus as Long and the author, found that histidine was deaminized but not decarboxylated, the end-product being an imidazole acid, possibly imidazole acetic, propionic, lactic or acrylic acid.

EXPERIMENTAL PART

In this part of the paper I have described the search for the products obtained when alanine and histidine are catabolized by the tubercle bacillus.

Metabolism of alanine: An ammonium-free medium was prepared according to the following formula: Alanine 17.8 gm., KH_2PO_4 2.6 gm., glycerol 100 cc., NaCl 10 gm., tap-water 2000 cc., and titrated to pH of 7. This medium was divided among 70 culture bottles, sterilized and inoculated with H37, a virulent human strain of tubercle bacillus.

At the end of three months' incubation a very heavy growth had been obtained, and the bottles were removed and filtered. Bacteriological examination showed the culture to be pure. Ten and one-half grams of dried bacilli were obtained from this growth. This medium gave a strong tuberculin test, did not give a biuret reaction, and was slightly acid (pH 6.6).

Removal and estimation of volatile aldehydes and acids: The medium

was concentrated *in vacuo* at 56°C. to a volume of 500 cc. The distillate was tested with $KMnO_4$ for reducing substance. No reduction took place, which eliminates the possibility of the presence of volatile aldehydes. The contents of the flask were then treated with 20 cc. of concentrated HCl and evaporated to dryness. The distillate was made up to volume, and a portion titrated with N/10 NaOH. The chloride content was determined by both Ag_2CrO_4 and Volhard's methods. The acidity found not to be due to HCl was equivalent to 32.04 cc. N/10 NaOH. The solutions containing the neutralized acids were evaporated to dryness, and a positive test for acetic acid was obtained by the basic iron-acetate method. This fraction did not reduce $KMnO_4$ in the cold, which indicates the absence of formic acid. The quantity of these acids was large enough to be of importance yet not enough to be fractionated.

Removal and isolation of nonvolatile acids: The dry residue from the removal of volatile acids weighed 125.0 gm., and was extracted with six 500 cc. portions of warm ether, the extraction requiring two and one-half hours. The ethereal extracts were combined and the ether evaporated, leaving a residue which weighed only 1.5 gm. This residue was dissolved in 50 cc. of absolute alcohol and divided into two equal portions. The alcohol was removed from one portion, and the residue treated with the theoretical quantity of pure brucine. A crystalline brucine salt was obtained weighing 0.87 gm., which after recrystallization melted at 247°–250°. The rotation of this salt was $[\alpha]_{20}^{D} = -23.6$. The melting point and rotation of this salt do not correspond to those of any of the known organic acids. The possibility of this being a salt of brucine and an inorganic acid is eliminated on the basis of the melting point and specific rotation. The quantity of this salt of unknown composition was too small for decomposition and analysis.

The second portion of the alcoholic solution of the residue, obtained by evaporating the ethereal extract, was treated while hot with 2 gm. of phenylhydrazine. As the solution cooled, long needles in rosette form crystallized out. The flask was then placed in the refrigerator for 48 hours, at the end of which time the crystals were filtered off, washed with absolute alcohol and dried in the air. These needles, which were a light pink color, melted at 209° and weighed 0.05 gm. The melting point was sharp, but it does not correspond to that of any of the hydrazones recorded in the literature or that were prepared.

Distribution of the nitrogen in the ether-insoluble residue: The residue

which was extracted with ether for the removal of the nonvolatile acids was dissolved in water and heated on the water-bath to remove all traces of the ether. This solution was then made up to volume, and analyzed to determine the distribution of the nitrogen. The methods employed were those of (a) Kjeldahl for the total nitrogen, (b) VanSlyke for amino nitrogen, and (c) Folin for the aeration of the ammonia.

	grams
Total nitrogen in medium originally	2.798
Total nitrogen recovered in the medium after three months growth of H37	1.900
Disappeared from medium	0.898

Analysis of the tubercle bacilli which had grown upon the medium showed the presence of 0.74 gm. of nitrogen. Inasmuch as 0.898 gm. had disappeared from the medium, 0.158 gm. is thus unaccounted for. The work of Bosworth (14), *et al.*, confirming the previous belief of Kendall, Day and Walker (5), suggests that in all probability this nitrogen was expelled into the air as ammonia during one phase of the growth of the microörganisms.

	grams
Nitrogen remaining in medium as NH_3	0.225
Nitrogen remaining in medium as NH_2	1.549
Sum of NH_3 and NH_2 nitrogen	1.774
Total nitrogen recovered in the medium after three months' growth of H37	1.900
Sum of NH_3 and NH_2 remaining in medium	1.774
Undetermined nitrogen in the medium	0.126

ACIDS FROM THE METABOLISM OF GLYCEROL BY THE TUBERCLE BACILLUS

A medium of the same composition as that used in the alanine experiment, with the exception that 4 gm. of $(NH_4)_2HPO_4$ was substituted for the alanine, was prepared and inoculated with H37 tubercle bacilli. By the end of three months the growth was very heavy. The bacilli were then filtered off and the medium subjected to exactly the same analysis for organic acids as in the case of the alanine medium.

The volatile organic acids obtained were equivalent to only 4.79 cc. N/10 NaOH. No test for acetic acid could be obtained. Nonvolatile acids were also present in quantities too small for estimation.

METABOLISM OF HISTIDINE

A medium for the following composition was prepared: NH_4Cl 4 gm., KNO_3 2 gm., KH_2PO_4 8 gm., NaCl 16 gm., $NaHCO_3$ 8 gm., $CaCl_2$ 0.2 gm., and 80 cc. of glycerol. These substances were dissolved in water and diluted to exactly 2000 cc. This is the nutrient medium No. III of Hanke and Koessler (17). Exactly 100 cc. of the above medium was transferred to each of 52 flasks. Pyrex Florence flasks of 300 cc. volume were used for this purpose. To each flask was then added 10 cc. of 2 per cent histidine dichloride solution and 90 cc. of distilled water. The pH of each flask was 7.2. The histidine content of a sample flask was determined colorimetrically and found to be 0.21 gm. The histidine that was used was a mixture of the mono and dichloride, which accounts for the 5 per cent excess in the color value over that which was presumably added.

These flasks were sterilized and inoculated with H37 and 1305, both being strains of virulent human tubercle bacilli. At the end of eight weeks a very heavy growth had taken place. One flask of each of the H37 and 1305 growth was removed for analysis. The pH of both flasks was 6.6.

Estimation of histamine: Both flasks were filtered, the microörganisms collected on paper and the filtrate treated with 1 cc. of concentrated H_2SO_4, and evaporated to dryness on the steam-bath. This residue was transferred to a precision cylinder with exactly 25 cc. of water. Ten cubic centimetres of this solution was treated with 3 gm. of solid NaOH. This solution was then extracted six times with 20 cc. portions of amyl alcohol. The amyl-alcohol extract was shaken with a strong acid solution, and this water extract was tested qualitatively for imidazoles. The diazo reaction was negative. Therefore histamine was not produced by these bacilli.

Estimation of remaining histidine: The alkaline solution which was extracted with amyl alcohol was transferred to a precision cylinder, treated with 7 cc. of concentrated HCl and diluted to exactly 25 cc. Five cubic centimetres of $CHCl_3$ was added to remove all traces of amyl alcohol. Colorimetric determinations for imidazoles were made on this solution, and the color value was calculated as histidine dichloride. The histidine content of the flask after the growth of 1305 was 0.18 gm., and

that after the growth of H37 was 0.168 gm. It is therefore evident that the consumption of the histidine by the bacilli was appreciable.

Isolation of products from catabolism of histidine: The contents of 22 flasks on which H37 had been grown and 23.87 flasks in the case of 1305 were filtered from the bacilli and used for the following analysis:

Removal of chlorides: Each medium was diluted to 3500 cc., treated with 1 cc. of HNO_3 and the chlorides precipitated with $AgNO_3$, and filtered.

Precipitation of imidazoles: The chloride-free medium was treated with an excess of $AgNO_3$ and 200 gm. of $Ba(OH)_2$ in 500 cc. of hot water. The solution was cooled in an ice-bath and the precipitate allowed to settle. The mixture was filtered on a Buchner funnel and the precipitate washed seven times with a cold saturated solution of $Ba(OH)_2$. The filtrate from the silver precipitate did not give a color reaction for imidazoles.

Removal of silver from the precipitate: The silver precipitate with the filter paper was thoroughly ground in a mortar with 300 cc. of 10 per cent HCl, after which 1000 cc. of water were added, and the mixture digested on the steam-bath for three hours. The silver chloride was filtered, washed seven times and pressed well on the Buchner funnel.

Precipitation of phosphotungstates: The filtrate from the silver decomposition was evaporated to dryness *in vacuo*, treated with 5 to 6 volumes of absolute alcohol, and evaporated again to ensure complete removal of free HCl. The residue was dissolved in 100 cc. of water, and the barium which was occluded in the alkaline precipitation removed with H_2SO_4. Enough of this acid was added to make the final solution 5 per cent in acid content. An excess of 30 per cent phosphotungstic acid in 5 per cent H_2SO_4 was added to the liquid, which was now amber in color, and the mixture digested on the steam-bath for forty minutes. At the end of this time the flask was placed in an ice-water mixture for 18 hours. The ice-cold phosphotungstates were filtered off, washed three times with the phosphotungstic acid reagent, and sucked dry.

Decomposition of phosphotungstates: The phosphotungstates with the filter paper were transferred to a large smooth mortar and macerated with little water until the mixture was a finely divided suspension. A hot saturated aqueous solution of barium hydroxide was added slowly until the solution was strongly alkaline to litmus. The contents of the mortar were then transferred to a flask and digested on the steam-bath for three hours to assure complete decomposition. The precipitated

barium phosphotungstate was filtered off and thoroughly washed. The excess barium in the filtrate was removed exactly with H_2SO_4 and the filtrate from the $BaSO_4$ concentrated *in vacuo* and diluted to exactly 100 cc.

Preparation of picrolonates of known imidazole acids: The picrolonates of histidine, imidazole lactic, propionic and acetic acids were prepared by the following method: One-tenth of a gram of the pure imidazole acid was dissolved in 10 cc. of water and treated while hot with the theoretical quantity of Kahlbaum's picrolonic acid in 10 cc. of hot absolute alcohol. The mixture was allowed to cool slowly, which resulted in the precipitation of the picrolonate. Complete precipitation was facilitated by placing the flask in the refrigerator over night. The crystals were then filtered off, washed with 10 cc. of cold absolute alcohol, recrystallized from 50 per cent alcohol, and dried in a vacuum desiccator. In each case the mother liquor was concentrated and a second crop of crystals obtained. The following melting points were obtained on these preparations (15):

	m.p.
Histidine monopicrolonate	232°
Histidine dipicrolonate	237°
Imidazole lactic acid picrolonate	219°
Imidazole propionic acid pirolonate	229°
Imidazole acetic acid picrolonate	249°
Imidazoleacrylic acid picrolonate	268°

The crystalline structure of the above picrolonates is not constant; however, they are usually obtained as needles arranged in rosette form. Of all the picrolonates prepared, that of imidazole acetic acid was the most insoluble in fifty per cent alcohol.

Preparation of picrolonates of the imidazole acids precipitated as phosphotungstates: Forty-cubic-centimetre portions of the solutions from the decomposition of the phosphotungstates, which had a volume of 100 cc., were evaporated to a volume of 10 cc. This volume while hot was treated with 10 cc. of 2 per cent picrolonic acid in hot absolute alcohol. The mixtures were allowed to cool gradually and finally placed in a refrigerator for 48 hours. At the end of this time the precipitated crystals were filtered off, washed twice with ice-cold absolute alcohol, dried in a vacuum desiccator, and recrystallized. The mother liquor was concentrated and a second crop of crystals was obtained.

Identification of the picrolonates: By fractional crystallization two

picrolonates having distinctly different melting points were obtained from both the H37 and 1305 media. In the case of the H37 medium 0.65 gm. of a picrolonate melting at 249°, and 0.2 gm. of one melting at 232°, were obtained; and from the 1305 medium 0.12 gm. of picrolonate melting at 249°, and 0.43 gm. melting at 232°. It is evident that these melting points correspond to the picrolonates of imidazol acetic acid, and of histidine respectively. Equal quantities of the picrolonate meltng at 249° and the picrolonate of imidazole acetic acid were thoroughly mixed. The melting point of the mixture was 247°, which is within the experimental error in melting-point determinations on picrolonates. The mixed melting point of the picrolonate melting at 232° with histidine mono-picrolonate was 232°.

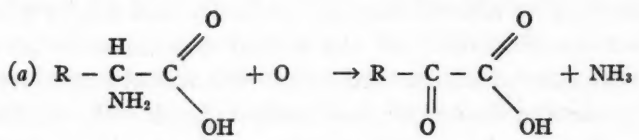
Both of the picrolonates isolated by this process had the crystalline structure of needles.

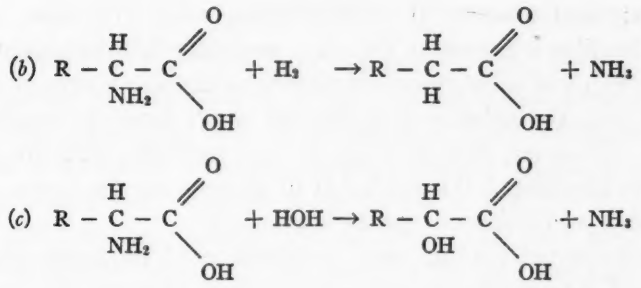
These two picrolonates were decomposed with lead acetate, and the lead removed with H_2S. The imidazole, the picrolonate of which melted at 249°, gave a strong diazo reaction and contained no amino nitrogen by the VanSlyke process. The imidazole, the picrolonate of which melted at 232°, also gave a strong diazo reaction, but the Van Slyke amino nitrogen determination proved this substance to be histidine. The color values when calculated as histidine checked the amino nitrogen value. The solution containing the imidazole, the picrolonate of which melted at 249°, was also examined by the quantitative colorimetric process. The color developed more slowly than is customary for imidazole acetic acid. The absorption by the lead sulphide was too great to make the colorimetric determination of any quantitative value.

Unfortunately, owing to an unavoidable accident, a complete combustion on the above picrolonates was impossible.

DISCUSSION

Theoretically, an amino acid may be deamidized by three methods, namely, (*a*) oxidation, (*b*) reduction, and (*c*) hydrolysis, as follows:

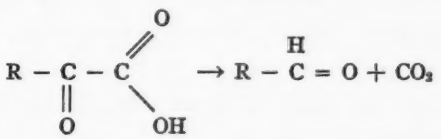




In the case of alanine these products would be (*a*) $CH_3CO \cdot COOH$ (pyruvic acid), (*b*) CH_3CH_2COOH (propionic acid) and (*c*) $CH_3CHOH \cdot COOH$ (lactic acid).

Long (12) found that propionates inhibited the growth of the tubercle bacillus. On that basis, propionic acid probably need not be considered, although, if present in the volatile acid fraction of the alanine medium, it existed in very dilute concentration. Long (16) also found that ammonium acetate did not support growth. In the light of the results of the present investigation this fact is perhaps to be correlated with the apparent nature of acetic acid as an end product of alanine metabolism.

The ketonic acids, such as pyruvic acid, are known to be very unstable, liberating CO_2 and going over to the aldehyde of the next lower series upon slight heating in weak acid solution, as follows:



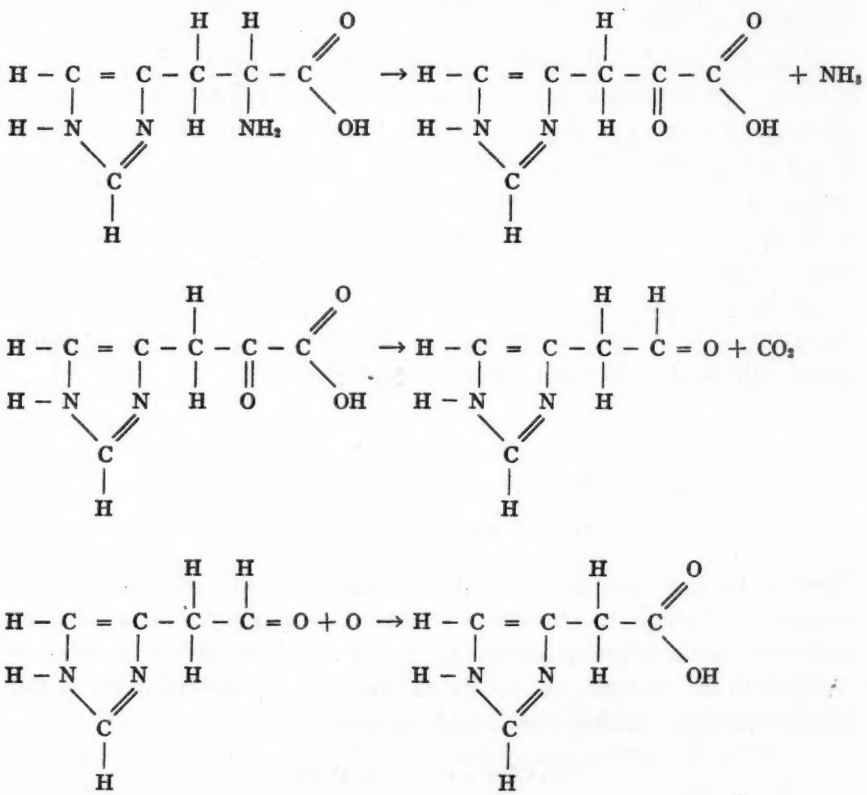
There is no evidence that the tubercle bacillus could accomplish this reaction, although it remains a potential possibility. However, the aldehyde (acetaldehyde) formed from the decarboxylation of pyruvic acid would be oxidized, as rapidly as liberated, by the oxidases of the tubercle bacillus yielding acetic acid, as follows:

$$CH_3\,CHO + O_2 \rightarrow CH_3\,COOH$$

In accord with this is the fact that no volatile aldehydes were obtained from the catabolism of alanine by the tubercle bacillus, and good evidence is advanced for the presence of acetic acid.

The practical absence of volatile acids, when the same strain of tubercle bacillus is grown on the same medium with the exception that $(NH_4)_2\ HPO_4$ was substituted for alanine as the sole source of nitrogen, indicates that the volatile acids did not result from the catabolism of glycerol. However, it is possible, but not probable, that the presence of alanine stimulated the oxidation of glycerol to the lower aliphatic acids, which would account for the acetic acid.

If a substituted alanine such as histidine (β imidazole alanine) is catabolized, one would expect the homologue of acetic acid to be produced, that is, imidazole acetic acid, as follows:



Evidence has been advanced for the presence of imidazole acetic acid, which is in accord with the above views, in histidine medium on which the tubercle bacillus had been grown.

SUMMARY

The metabolism of alanine (amino propionic acid) by the tubercle bacillus yielded volatile acids in appreciable quantities, of which acetic acid was the predominant one. From the nonvolatile acid fraction small quantities of a brucine salt and a hydrazone were obtained, neither of which was identified. Volatile aldehydes were absent. Of the total nitrogen added to the medium 0.158 gm., or 5.65 per cent, was probably expelled during growth. After the growth of the microörganism, 0.126 gm. of the nitrogen remaining in the medium could not be accounted for as ammonia or amino nitrogen.

In a medium in which alanine was not present and ammonium phosphate was the only source of nitrogen, acetic acid was not produced, and other volatile acids, as well as nonvolatile ones, were present only in exceedingly small quantities.

In the metabolism of histidine (α amino β imidazole propionic acid) the tubercle bacillus produced an imidazole acid, which seems to be imidazole acetic acid, although the evidence is not entirely conclusive. Histamine was not produced. In the course of this work the melting points of the picrolonates of the imidazole acids, which do not appear to be on record in the literature, were obtained.

CONCLUSIONS

On the basis of the above experiments, the evidence points toward acetic acid and imidazole acetic acid as being the catabolic products from the growth of the tubercle bacillus on alanine and histidine respectively, with the possibility of the corresponding ketonic acid being the intermediate product.

The author wishes to take this opportunity to thank Dr. E. R. Long and Dr. Milton T. Hanke, whose most hearty assistance has made this work possible.

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ADDRESS OF THE PRESIDENT[1]

CHARLES J. HATFIELD

It has been the custom for the President in his annual address to review the events and developments of the year that is past and to point out the lines upon which future progress should logically be formed. It is an inventory or stock-taking and a determination of a plan of operation, and it seems to be worth while.

Our Association is stronger in organization and financial support than it has ever been. The Executive Committee has been faithful in attendance at all meetings, and has given its best thought to the carrying out of the approved policies of the Association. The work of the various committees of the Board of Directors, and the joint groups of directors and secretaries, has been faithfully and efficiently performed. Under the able leadership of the Managing Director, the Executive Office has supplied increasingly effective service to all parts of the country. The teamwork and coöperation on the part of every element in the Association has never been so marked. The spirit of service to the whole, rather than insistence upon the necessities of any part, has been constantly emphasized and approved. Each year it becomes more evident that North and South, East and West, can understand each other and coöperate. We are indeed speaking the same language.

Although the complete returns from the census for the registration area are not yet available, our statisticians are confident that the mortality rate from tuberculosis in all forms will again show a marked decline. The reasons for this continued drop are not yet clearly understood. The writers who attributed the decrease in 1920 and 1921 to the influenza epidemic, on the ground that many cases of tuberculosis were swept away in the tremendous waves of respiratory affections, and who predicted that after a few years the mortality rate for tuberculosis would again rise, are quite at sea. It seems improbable that the effects of the influenza epidemic have anything to do with the mortality rate six years later. On the other hand, the explanation that the rapid increase in public

[1] Delivered at the twenty-first Annual Meeting of the National Tuberculosis Association, Minneapolis, Minnesota, June 17, 1925.

health organizations and in popular understanding of health measures, and the consequent improvement in community and personal hygiene are responsible, seems more and more satisfactory. It is clear, also, that the public health programme has been materially aided by the anti-tuberculosis work. The measures that prevent tuberculosis certainly help to build up resistance to other diseases, and it is fair to assume that the tuberculosis campaign has had a direct effect on the mortality rate. Therefore, in the speaker's opinion, the National Tuberculosis Association, through its affiliated associations, may justly claim an important part in the decline. Certainly no line of public endeavor has ever had greater reason for encouragement in the way of results that are patent and acknowledged by all.

The prosperous condition of the National Tuberculosis Association, both as to organization and results, is due to two principal factors. We have been favored from the beginning by an unusual group of leaders, medical and lay, from all parts of the country. The men and women who have been important factors in the development of the policies upon which we have prospered have not been impractical theorists, but have been those whose interests have been in line with efficient public service. They are often described as self-sacrificing friends of humanity, whose services are given at great personal sacrifice and in angelic spirit. It is far more accurate and more reassuring to believe that our friends, past and present, are happily those whose ambitions point to group organization and public benefits; who are not indifferent to recognition, but who prefer that such recognition in position and other reward shall be in line with their chosen work.

Our Association has been fortunate in its friends; but these friends and leaders would have been able to do little without financial backing: this has come from the Christmas Seal. The story of the Seal has been often told, but with each successive year it grows more wonderful. In 1917 we rejoiced in selling $1,800,000 worth of seals. In 1924, seven years later, the sales were almost $4,500,000. This increase has been hastened by war experiences, but the foundations upon which the present sales are organized are not ephemeral; they are based on practical and broadly useful services to the communities where Seals are bought, conducted on a programme and budget meeting general approval, and with strict accounting for money received. Upon these foundations has been built a remarkably efficient method of sale, developing each year through pooling the experience of all. In 1924 the returns averaged

four stamps for every man, woman and child in this country. Who will venture to predict the future limits of the Seal Sale?

One development in the field of local philanthropy has caused anxiety in relation to the Sale in certain parts of the country. The rapid spread of the community-chest method of financing charitable and philanthropic work has been very marked. The advantages of the Community Chest are obvious,—one drive for all, and consequent economy in raising funds, standardization of management, and stimulation of everyone in the community to do his share, resulting in an increase in the amounts given and in the number of contributors. The tuberculosis workers must sympathize with and approve of the community-chest idea. When, however, it is proposed that the local tuberculosis association shall become a member of the Chest and shall give up or modify the Seal Sale, the results of such union should be carefully considered. In the first place, the Sale represents the most important and effective educational campaign of the year for the prevention of tuberculosis and the promotion of public health. At least one-half of the cost of the Sale is rightly charged to the educational phase. When the local tuberculosis association becomes a member of the Community Chest, this educational feature is partly or wholly lost. Moreover, the effectiveness of the campaign against tuberculosis is largely dependent upon the close interlocking of local, state and national endeavor. At the present stage of development the Community Chest is primarily concerned with financing local enterprises, and in lean years the support of state and national work seems to be impossible. Also, the Seal Sale is a unique system of financial and educational Campaign, reaching the youngest and poorest individuals of the population who are not reached by the Community Chest. It must be remembered that the Seal Sale was an accepted method of raising funds and of educating the public long before the first Community Chest was thought of, and has in time been accepted as a voluntary tax for health at the time of Christmas. Actual experience has shown that in many Chest cities the conduct of a Seal Sale has been found *not* to interfere with the collection of funds for the Chest, but rather represents a valuable additional source of support for social endeavor. Lastly, conservation of the integrity of the Seal Sale may in the future be of vast importance to general health work other than tuberculosis. It is possible that with the broadening of the programme of tuberculosis associations the Seal Sale may be of great value in financing oher forms of health preservation, and must therefore be carefully conserved.

The considerations stated above indicate clearly the policy of the National Tuberculosis Association in relation to merging with forms of combined fund-raising. Our affiliated and local associations should be advised to coöperate with their local community chests in every way, *except* the joint raising of funds. They should be members of the councils of social agencies, and join in the complete coördination and development of the local work, but they should retain the Seal Sale. In localities where it has been found necessary for the tuberculosis association to merge with the Chest, the tuberculosis agency should make every effort to convince the Chest officials that the Seal Sale should be conducted as an auxiliary to the Chest drive, and with the usual provision for the support to be given to state and national work. When the sale is not so conducted, services to the community—educational and otherwise—are lost beyond replacement.

It is a matter of interest to note the broadening of the policies of the National Association, beginning with its organization in 1904. For the first few years the chase of the germ was vigorous through antispitting campaigns, sanatorium construction for the care of improvable patients, and stimulation of public interest by lectures and exhibits. After the Congress of 1908, isolation of advanced cases was stressed and eradication of bovine tuberculosis was advocated. Later still, building up of resistance, especially in children, was emphasized. While Dr. Farrand was still in charge of the Executive Office the relationship of tuberculosis to general public-health work was clearly recognized, and definite duties in coöperation with the American Public Health Association were assumed. Prior to and during the War. the connection with Federal departments interested in health was recognized and developed. In 1920, the plan for the National Health Council was studied, the field was surveyed, and in the following year our Association was active in promoting its organization. The National Health Council was frankly considered a tentative step toward the formation of a National Health Association.

Since our National Association was and is the most powerful and strongly organized voluntary health organization in the country, it has been suggested that its name be changed to the National Health Association, that it take other voluntary health organizations under its wing, and that it develop the Seal Sale and other means of support, so as to be able to finance diversified forms of health work. Such a change of policy has seemed inadvisable for various reasons. Our first concern is the control

of tuberculosis; that job is not complete, and cannot be for years to come. Singleness of purpose not only develops our own strength, but through that strength makes us more able to help other lines of work. A diffusion of interest would weaken and perhaps jeopardize progress toward our goal. We have not had the funds or the prospect of support sufficient to finance diversified work. On the other hand, the continuing decrease in tuberculosis and the development of machinery for its control seem to point to a time in the not distant future when our Association can consider the gradual broadening of its field; and here is where the National Health Council becomes an important factor in the situation. The Council has made quite definite progress during its first few years of work. It has brought together under one roof and in combined service the executive offices of most of its members. This one thing has done more toward a better understanding than has any other single feature. It means that the members of the Council are learning to trust and to depend upon one another.

Consciousness of these developments has had a noticeable effect upon the policy and programme of the National Tuberculosis Association and its affiliated societies. A number of the affiliated associations have changed their names to Public Health Associations, while still confining their activities to antituberculosis work. Some years ago, all Child Health endeavor was included in the definition of antituberculosis work. During the past year the prevention of cardiac disease has been included under special conditions, and generalized nursing associations have been helped. The plan of gradual extension seems to be in line with the thought of the past decade. The present attitude of our Association toward this important future development may be expressed by a paraphrase of the words of St. Paul: *Not forgetting the things that are behind—we press forward.*

To the members of the National Tuberculosis Association who are familiar with the Bible, the increasing interest of the tuberculosis workers in the research programme must suggest another text from St. Paul: *Whatsoever things are true.* The developments of the past few years in relation to the study of special problems of the disease have met with instant approval on the part of the majority of our members. Of course, the investigative spirit has been active in our Association since its beginning. All are familiar with Dr. Trudeau's words in the first Presidential Address: "The practical application of knowledge already gained as to the measures which respresent prevention, is one of the two great

responsibilities of the National Association. The other is the extension and advancement of the study of tuberculosis in this country. The United States, at any rate so far as tuberculosis is concerned, should not much longer lie under the imputation of being 'one of the largest borrowers in the scientific markets of the world.'"

The *Transactions* bear witness to the fact that in every department of work, in clinical and sociological lines as well as among the laboratory workers, the investigative spirit has been present, and valuable contributions to diagnosis, treatment and social methods have been made. To all of us it is clear that such spirit is the source and mainspring of progress. On everyone in the tuberculosis field, whether physician or layman, there is the obligation to add something, however little, to the sum of existing knowledge. It is in this spirit of building up, little by little, the store of proved facts, filling in the gaps in our knowledge, that the research programme of the Association has been developed. A specific cure for the disease may not be found in our day, or through our activities, but we can have the satisfaction of helping to build the foundation of facts which will give future students an advanced start. Reports will be placed before this meeting of progress made by the distinguished men working with our Committee in their special fields of anatomy, bacteriology, chemistry, biology, and the roentgen-ray. Every problem is of interest and its solution directly or indirectly affects our conception of the disease. This is not the occasion for a detailed discussion of the research problems and their meaning to all of us. But it is fitting that we express our interest in them and our approval of the plan by which the most competent and authoritative men in the special lines in which tuberculosis research is particularly needed are performing for our Association these great services.

Within the year just past we have been interested in the report of a successful treatment of tuberculosis by the injection of a mineral preparation, as announced from Denmark. In this case, the test of science as applied to the treatment has rendered a verdict of "not proven." We must remember that the standards by which any new discovery is measured are: First, the records of the successive steps must be so complete that their logical progress from accepted facts to newly discovered data can be passed upon; and, secondly, the same results must be secured when the prescribed steps are carried out by other experts. The modesty of workers in fields of research is often misunderstood. Their hesitancy in accepting the announcement of a new discovery is sometimes ascribed

to jealousy or to a disinclination to give credit where due. When we understand upon what a basis of established fact new procedures must be judged, and what prolonged labor is necessary to test the results by repeating the experiments, we can better appreciate their position. Since, moreover, we have learned by bitter experience the evil resulting from too ready acceptance of procedures that are not sound, we shall be content to wait with patience for confirmation of the value of any announced "cure."

The above considerations lead naturally to the question as to whether publicity is under any circumstances an advantage to research work. Certainly the announcement of new discoveries that have not been thoroughly tested, or of wonderful plans that are still to be carried out, can do great harm. All of us condemn such measures. On the other hand, investigation must be made popular. The public must be educated and interested in order that support may be forthcoming. Perhaps our rule should be to insist that public announcements shall be restricted to results that have been thoroughly tested and accepted, and that nothing should be said about experiments not yet completed. There is more than enough in the way of past accomplishment to equip any speaker or writer who desires to stimulate public interest in research.

In this connection, it seems fitting that we express our appreciation of the fine service rendered to the tuberculosis field by our AMERICAN REVIEW OF TUBERCULOSIS. Through the genius of Dr. Krause the Review stands to-day as the foremost periodical in the English language dealing with the scientific side of tuberculosis work. It is the peer of any scientific journal that is devoted to a medical speciality.

In October of the coming year we are expecting to welcome to this country the *International Union against Tuberculosis*, which at present includes representatives of nearly all the countries that are members of the League of Nations, and the United States. Our Association took an active part in the formation of the Union in the years immediately succeeding the World War, and has been represented at each of the meetings since held. For the coming session our Board has approved a plan which should be successful in securing the presence of many of the great figures in tuberculosis work, especially from the European countries. We can be certain of a distinguished and authoritative Conference. We must make certain, also, that the arrangements for the meeting shall be characterized by the dignity and distinguished hospitality that have marked conferences in Paris, Brussels and Lausanne. Arrangements

have been made for our Managing Director to attend the meeting of the Executive Council in Paris in July of this year, and we can be sure that his familiarity with the personalities involved, and his trained diplomacy will secure for our meeting the best possible attendance.

It is probable that important matters will be brought up for decision,—perhaps the most important being the question of the admission of Germany to the Union. It is the opinion of the speaker that favorable action on this point is indicated. Science and the health of the world have no political boundaries. Personal antagonisms are dulled by time. Germany has a definite contribution to make in the field of research. An "International Union" that excludes a strong body of workers in the common cause is unworthy of the name. There is no chance of the assumption of authority on the part of the new member, such as was felt in the old International Conference whose offices were in Berlin, and in whose administration German influence was predominant.

Our Association can look for definite benefits from this international gathering. Many of our members may not be able to attend the formal conferences, as only members of the Union are invited. But it is expected that our distinguished guests will take part in the programme of our own Annual Meeting, to be held immediately following the International Union; and it is hoped, also, that it will be possible for local groups to arrange for visits to their own cities of various guests who may have messages of especial interest to their people.

In conclusion, there remains to the speaker the pleasant duty of thanking the Association for the great honor it has conferred in electing him as presiding officer for the year that is past. The work with the Executive Office, the other officers and the members of the Association has been a constant pleasure and will always be gratefully remembered. From the point of view of the retiring President, there is no doubt whatever that the National Association can look forward to the immediate future with confidence in its organization, and with enthusiasm and inspiration in view of its logically broadening programme.

EXTRAPLEURAL THORACOPLASTY FOR PULMONARY TUBERCULOSIS[1]

HOWARD LILIENTHAL[2]

Selecting from the various surgical procedures which are recognized as legitimate in dealing with tuberculosis of the lungs, I shall speak solely of that known as multiple extrapleural paravertebral costectomy. The object of this operation is to produce some degree of collapse of the lung and to bring about rigidity of the entire hemithorax. This rigidity is quite as vital as the pulmonary collapse, because rest is the main factor in the cure of tuberculosis and this procedure reduces to a minimum the movements of respiration.

In an apparent effort of nature to produce spontaneous cure there is pulmonary fibrosis with contraction; the ribs become approximated and their direction takes on an increased obliquity. The mediastinum is drawn into the affected hemithorax, often with great angulation of the trachea and displacement of the mediastinal contents including the heart. The diaphragm is drawn upward, limiting still further the chest volume. When this condition has been brought about by disease, however, it rarely develops far enough to accomplish complete rest for the tuberculous breathing apparatus. There is also a constant and injurious tension upon the more movable abdominal and midthoracic septa.

The surgical fixation of the chest has been conceived along the natural lines of recovery. The simple expedient of dividing the ribs posteriorly permits them to assume an exaggeratedly oblique position, thus bringing them nearer to the central line of the body; and the tension, especially on the mediastinum, is relieved even though that space with its contents should not swing back to its normal position after the operation. In most of my own cases the added factor of diaphragmatic paralysis has been secured by an operation upon the cervical portion of the phrenic nerve.

[1] Read before the American Climatological and Clinical Association, Washington, D. C., May 5, 1925.

[2] 52 East 82nd Street, New York City.

I have spoken of dividing the ribs. As a matter of fact, this division is accompanied by resection of bone but it must be remembered that rigidity, rather than compression, is the desideratum. The mere removal of large sections of the thoracic cage will not necessarily have a correspondingly better effect than the shorter costectomies, because the free motion of the widely resected ribs continues with respiration, sometimes for a long time before synostosis takes place. I believe that in performing this operation one can commit the error of removing sections which are too long, and that osseous regeneration is thereby either greatly delayed or may even never occur. Then, of course, we lose much of the advantage of the rest accomplished by rigidity.

After paravertebral thoracoplasty there is immediate reduction in the capacity of the affected pleural space, but rigidity develops more slowly. The ribs will usually have regenerated in about four weeks, but even after this there is further cicatricial contraction which may progress for a number of months. Still, to illustrate the importance of rigidity over mere reduction in chest volume, I may cite two patients who show comparatively little contraction, but such pronounced fixation that the corresponding lung is practically functionless and the clinical results are fully as good as those in which an ideal anatomical collapse has been secured. This is in contrast to the effect produced in artificial pneumothorax. Here the greater the pulmonary compression the less the respiratory motion, air being elastic.

The phenomena of convalescence in an ideal case appear with great rapidity. Within two weeks of the operation the sputum and cough diminish, the temperature declines and the individual has a sense of well-being. Indeed, it is sometimes difficult to hold the patient down to the necessary hygienic rules which must govern his mode of life long after he has recovered from the mere surgical procedure; for, after all, he still has tuberculosis, and the danger of its pathological progress, either in the lung which was operated upon or in its fellow, is present until there is a true arrest with fibrosis or, still better, calcification. The surgeon should therefore insist upon the patient's return to the sanatorium from which he came, or at least to the practice of the hygienic measures which have become the mainstay of phthisiotherapy.

To summarize, we may say that this operation provides conditions under which fibrosis and arrest are facilitated. It is applicable in two main divisions of pulmonary phthisis: first, when healing would be otherwise impossible and the immediate prognosis is bad; and second,

when the progress toward arrest is so protracted that the outcome is in doubt and many more years of invalidism may be expected.

There are certain dangers connected with this method of therapy which will now be discussed.

The accidental violation of the pleura is uncommon provided the operator is careful in dissecting the periosteum from the bone. If, however, the pleura should be opened, the danger is not necessarily great. To be sure, when purulent pleurisy is present the wound will become infected, but the production of collapse need not be interfered with.

Injury to the structures in close relation with the first rib, especially the subclavian artery and perhaps more particularly the brachial plexus, should be avoided by extreme delicacy of dissection.

Hemorrhage: The quantity of blood lost varies with the individual case. It is apt to be greater under general than in local anaesthesia. However, the choice between general and local anaesthesia depends on factors which need not be discussed here in detail, although it may be said that in making the selection the temperament of the patient must be taken into account. At any rate, the possibility of blood transfusion, preferably by the direct method, robs thoracoplasty of one of its dangers. I have also noted that it lessens the period of convalescence and contributes greatly to morale. Whether or not transfusion is to be employed it is essential that the necessary preparations be made for carrying it out.

Shock rarely follows this operation when it has been performed in two or more stages and, as in all surgery, the greater the blood loss the more profound is the shock. Still, there are other factors which contribute to pure shock, especially the sudden alterations in the position of the mediastinal organs. While this change may also occur in cases treated by pneumothorax the immediate effect of the mediastinal displacement is not so pronounced as it is after the major procedure.

With an easily movable mediastinum both pneumothorax and thoracoplasty may be followed by the sudden impairment of function in the opposite lung from purely pneumatic conditions, and also because of changes in the circulation. This may result in a lighting up of the quiescent process in the good lung due to autotuberculinization from toxic substances forced into the lymph channels, or from vascular congestion. In nonsurgical as well as in operative wounds of one hemithorax, even in perfectly healthy individuals, congestion and oedema, often fatal, have been observed. The condition was unfortunately

far from rare in the open thoracic injuries encountered during the war. In one of my tuberculosis cases these phenomena appeared. There was immediate relief on loosening the dressings and recovery followed. The patient was a woman who had a fibrinous and cavernous condition of the right lung. There had been for some months quiescence on the left (slightly affected) side. After the phrenic-nerve avulsion and resection of the upper five ribs there was no untoward symptom; but a few hours after the remaining ribs had been resected at another stage, dyspnoea, rapidity of respiration, and great cyanosis with weakness of the pulse were seen. On completely removing all pressure by the dressings on the side of operation relief was spectacular. This happy result was doubtless due to the subsidence of the conditions just referred to, including the return of the mediastinum toward its normal place. The same picture was presented in at least two other of my cases. Manifestly, in the presence of activity in the opposite lung these dangers are much increased. They are not common when it has been in a state of quiescence for three or four months. It is therefore apparent that one of the most important observations to be made, when thoracoplasty is contemplated, is of the extent and activity of the tuberculous condition in the other lung.

It is decidedly unsafe to predict the possible effect of an operation unless we have an accurate history of the course of the disease for at least one month preceding. At a single observation it may not be possible to determine whether a lesion is advancing or receding, while after a few examinations, days or weeks apart, the facts can be established almost with certainty. It would be the height of folly to operate in the presence of an advancing lesion of the opposite chest. It would also be unwise to undertake surgical treatment too soon after recession has begun. It may, however, be taken for granted that no operation should be performed if there is even remote hope that the tuberculous lung may ever be permitted to resume its function.

Excessive fever need not be a contraindication to thoracoplasty, because soon after a successful operation the febrile condition may be expected to subside.

The presence of air or fluid, whether purulent or not, in the diseased side may modify the order of precedence in the operations but does not forbid surgical therapy. When empyema, tuberculous or mixed, is present, with or without accompanying pneumothorax, the danger of thoracoplasty preceded by drainage is less than thoracoplasty upon an uncollapsed lung.

Embarrassment of respiration and cardiac action on account of *traction upon the mediastinum* would make an operation all the more advisable. Indeed, even in the presence of a healed tuberculosis, thoracoplasty may relieve the circulatory distress which often accompanies mediastinal deviation.[3]

When hemoptyses are frequent or copious, and artificial pneumothorax cannot be produced on account of adhesions or dense pulmonary infiltration, collapsing thoracoplasty is the measure which most logically comes to mind. Something must be done to check the bleeding, and great reduction of lung volume is not necessary for this purpose.

Another reason for advising surgical collapse is when pneumothorax treatment has been continued for years and reëxpansion is invariably followed by an exacerbation. Here the dangers arising from pulmonary compression are not as great as usual, since the lung was presumably well collapsed after each refill, and the operation becomes merely a plastic in which the chest-wall is made to take the place of the air but with the added advantage of far greater rigidity than could be secured by air alone. These patients deserve to have the case put clearly before them, and they should cast the deciding vote, for, after all, the pneumothorax may be continued indefinitely as long as pleural infection is absent.

The advisability of operation in the presence of other disease: The presence of tuberculous lesions in other parts of the body does not necessarily contraindicate the surgical treatment of the pulmonary condition. It may even make it more imperative; for example, in the case of laryngitis and enterocolitis in which the subsidence of the pulmonary lesion has a strong tendency to diminish infection by contact with the germ-laden sputum. There is a certain analogy between this and the spontaneous disappearance of vesical disease after the removal of a tuberculous kidney.

Osteomyelitis and arthritis may be treated independently of the operation upon the chest; but unless these lesions are so far advanced that of themselves they threaten life they should not form a contraindication to thoracoplasty. Certain lesions of a nontuberculous nature may, however, forbid the operation on the chest; for example, incurable malignant tumor, bacterial endocarditis, some primary diseases of the blood, etc. This is merely a matter of common sense. There is no use

[3] This indication for operation was first called to my attention by Dr. J. Burns Amberson, Jr., of the Loomis Sanatorium.

in attempting by surgery to arrest the tuberculous pulmonary lesion if the patient must in any event succumb to another disease. There are border-lines, however. Without going into the matter exhaustively, I may mention amyloid disease. When not too far advanced it is quite probable that the elimination of the cause (the chronic suppurative process) may bring about a great improvement, or perhaps even the disappearance of the amyloid condition.

In deciding upon operation, its advisability as well as its character, it is essential that there be free discussion between the representatives of the medical and surgical branches of the profession. With the aid of X-ray examination and clinical signs, together with the history of the case and especially of its progress, the suggestion of operative therapy will be mainly the concern of the phthisiologist. The type of surgical procedure should be agreed upon by both. The almost universal fear of physicians that a person with tuberculosis makes necessarily a poor surgical risk must be overcome, because as a matter of fact this is far from true.

The patient should come to the surgeon with the statement from his physician, preferably a phthisiologist, that further treatment without operation may be considered futile and that the function of the opposite lung and its condition are satisfactory.

Now comes what is, perhaps, the fundamental part of our discussion; namely, the question of refusing surgical intervention because of it; apparent immediate dangers, even assuming that there are no positive contraindications such as the presence of another and incurable diseases and also assuming that there is one lung which is able to function well enough to sustain life indefinitely. So long as it has been determined beyond a reasonable doubt that there will be a fatal outcome within the near future, say in from three to six months, the matter becomes largely one of the temperament and character of the surgeon,—his willingness or unwillingness to take desperate chances in otherwise hopeless cases; and this brings up the matter of so called statistics. Tables with figures drawn from the vast experience of a multitude of reporters are of great value in determining facts relating to mortality, cure, operative recovery, etc.; but they are often of little service when we are confronted with a particular case. Mere descriptions, even with clinical and radiographic records, cannot bring about the visualization of the patient as an individual. It is necessary to have seen and examined him in addition to knowing the bare facts of his illness; to have estimated

his resistance to surgical trauma and to the immediate physical changes brought about in the vital organs by the operation itself, not to speak of the psychic element, by no means the least in importance. All this can be but vaguely surmised before the final and irrevocable test; and here will come the influence of vision and of experience with other cases of a similar type. Again, to refuse to operate merely because of a given calculated percentage of mortality does not seem fair. The final affirmative decision can only be reached after weighing all the ascertainable facts and considering the authoritative opinion of the phthisiologist that otherwise death will soon follow.

My own opinion is that the principles involved are those of surgery in general, whether we are dealing with tuberculosis of the lungs or, for example, advanced acute appendicitis, except that the element of urgency is, as it were, on a lower plane. It is inconceivable to me that operative aid should be withheld in the acute abdominal disease even though the patient appear to be almost moribund, and in tuberculosis the same arguments hold; in fact, the prognosis in one of these old cases of phthisis may be much more accurately forecast. Therefore I have never refused my services in any case in which there was one sufficiently healthy lung and the phthisiologist had predicted a rapidly approaching fatal termination. To be sure, a number of these patients have died, usually from postoperative autotuberculinization and from acute conditions in the better lung, but others who had been literally given up and who might have been expected to have died within a few weeks without surgical intervention have made brilliant recoveries. It seems to me that to achieve one success like this justifies a considerable number of so called failures. But let us again revert to the comparison with appendicitis. I can well remember when only suppurative peritonitis, local or general, seemed to justify a laparotomy, while now the mere making of the diagnosis points to the therapy. In tuberculosis with one lung *irretrievably* diseased—mark the expression—it should be considered bad surgery and therefore bad medicine to put off, not the evil day, but the hoped-for deliverance.

A PROGRAMME OF RESEARCH ON THE ACTION OF LIGHT ON LIVING MATTER

WITH SPECIAL REFERENCE TO APPLICATION IN METHODS OF THERAPY[1]

BRIAN O'BRIEN

The effects of light on growth and metabolism, and its stimulating and destructive action, have been extensively studied. Specific information, however, is lacking, and investigations in this field thus far are too generalized in their methods to definitely predict cause and effect. As a result, the principles underlying the physiological action of light have been very little understood, and even clinical interpretations on an empirical basis have seldom been accurately drawn. Claims have been, and are being made, for a number of forms of light treatment with little exact information to substantiate them, and very naturally there is skepticism in the absence of exact information.

In spite of this the possibilities in this use of light cannot well be overlooked. Some very excellent and encouraging results have been obtained, most strikingly perhaps in rickets, and notably also in all extrapulmonary forms of tuberculosis, in various nontuberculous skin conditions, and in such systemic infections as osteomyelitis.

The destructive action of light on bacteria and other elementary microorganisms has been known for some years. As early as 1877 Downs and Blunt, in three papers presented to the Royal Society on *The Influence of Light on Protoplasm*, reported the destruction of putrefactive bacteria by sun and diffuse light, and made rough measurements of the relative action of different colors. Since that time over ninety investigators have published more or less extensive work in this direction, but many phases of this problem are still unsolved and even the lethal light dose for the tubercle bacillus has not been properly established. The possibilities of the prophylaxis of dwellings and public buildings from information in this direction alone are very great. Knowledge such as this may change existing building codes.

[1] From the Mrs. Joseph T. Jones Research Fund of the Buffalo Tuberculosis Association, J. N. Adam Memorial Hospital, Perrysburg, New York.

In view of this, as well as the many important results being obtained in photochemistry, and the extensive information which light physics is yielding in the field of atomic and molecular structure, there is ample justification for fundamental research in the reactions of life to light.

This outline is presented in the hope of stimulating more interest among investigators in related fields, and of obtaining more unified research following some definite programme.

The problem of investigating the physical and chemical effects of light, or more broadly electromagnetic radiation, on living matter is of necessity very diversified. Basically it is physical, and measurements, methods and precautions must be treated as such; but the problem is not one which can be solved by a physicist working alone, nor for that matter by any one man or any one field. Certainly, investigators trained in physiology in its various aspects, including the chemical, are of prime importance in this, and research workers in certain other directions may be necessary, as will appear from a consideration of the outline following.

This outline requires certain remarks in explanation. As already stated, a considerable amount of work on the biological action of light has been done. In only a few cases, however, has the light used been properly measured and standardized, due perhaps to the fact that investigators in this field have not, for the most part, been primarily interested in light, and to the difficulties involved in such measurements. In addition, therefore, to filling in the many gaps existing in this field, much of the work already done should be repeated.

For the moment, leaving polarization phenomena out of the question, we may completely define a beam of light, or in general of radiation, in terms of its total energy and the spectral distribution of that energy, and these are the two quantities which we must measure in every case. Before discussing the precise methods by which this is to be accomplished, the spectral regions to be covered in this investigation must be considered.

The known electromagnetic spectrum extends from the shortest gamma-radiations from radioactive substances out through X-radiation, ultraviolet radiation, visible radiation, infrared radiation, to the longest known electric waves such as are used in radio communication. In this range there are only two short gaps which have not been experimentally investigated by physicists, the one separating very long wave-length X-radiation from very short wave-length ultraviolet (some are of the opinion that this has already been bridged), the other separating

very long infrared radiation from short electric waves. There is reason to believe that electric waves such as are used in radio communication are without direct physiological action. Until investigations on the biological action in this region seem more promising than at present, they had better be omitted. On the other hand, the region between the shortest wave-length ultraviolet (about 100 A.) and ultraviolet of wave-length 1850 A. has been shown to have certain interesting effects on lower organisms. This region is absorbed, however, in passing through even a fraction of a millimetre of air, and so is not met with under any natural or ordinary conditions. Investigations here must be conducted entirely in a good vacuum, and of necessity only on elementary organisms. While biological action in this region may later prove very interesting and even valuable, it is believed that work in this direction will not be profitable at present.

It is proposed then that the investigations deal with biological effects in the electromagnetic spectrum from short gamma-radiation out to as long wave-length X-radiation as will still travel a considerable distance through air (about 20 A.), stop here, and take up the electromagnetic spectrum again at 1850 A., the shortest ultraviolet that will travel through appreciable air-paths. From here the spectrum can be covered without a break through the remainder of the ultraviolet, through the visible, and out to long wave-length infrared.

The first part of this field, the action on living matter of the X- and gamma-radiation region, has been given relatively more careful attention by a great many investigators than has the second part, that extending from the moderately short ultraviolet through visible to extreme infrared, or "light" region as the term is commonly used. In view of this and the far more extensive occurrence in nature of the latter region, it is this latter that we propose to emphasize chiefly in the work outlined here, though the former cannot be neglected.

We shall consider first the methods of measurement of the "light" region. For the measurement of the total energy in a light beam, per unit cross-section and unit time, some form of total radiometer is required. With light sources of fair intensity anything may be used, from a properly calibrated blackened bulb thermometer (not screened by material opaque to the beam in question) to more elaborate and precise devices such as the pyrheliometers of Abbot. Such instruments are easily calibrated in absolute units by direct comparison with a previously calibrated radiometer, by exposing to an artificial black-body radiator of known

effective area and temperature, or from their previously determined thermal constants. These measurements present no very great difficulties.

The measurement of the spectral distribution of energy in a light beam is somewhat more complicated. It requires, first, that the light be suitably dispersed into a spectrum and, second, the determination of the energy in the various portions of the dispersed beam or spectrum. This can be accomplished by the use of an absorbing or "gray" wedge in front of the collimator slit of a spectrograph with a photographic plate as receiver (a very convenient method over a limited spectral range), but this depends on knowledge of any departure from true "grayness" in the wedge, and, like the more laborious photographic method of measuring plate densities without a wedge, is restricted in range and open to the objection of depending on the sensitivity-wave-length curves of the emulsions used. A more universally applicable method (the one which we are using for the most part) is the separation with an exit slit of a sufficiently narrow region of the dispersed beam or spectrum produced by the spectrometer, and the measurement of the total energy in that region with some form of microradiometer.

For the dispersion of the light beam and the measurement of wave-length, some form of spectrometer is of course necessary. For the type of work outlined here prism instruments, although secondary standards, possess many advantages over grating instruments, and need be calibrated only once. They should be preferably of a constant deviation type, because of the greater ease of mounting the microradiometric apparatus, and their greater convenience when used as monochromatic illuminators. In order that the whole spectrum may be covered from wave-length 1850 A. out to the extreme infrared, at least two spectrometers are required, the ranges of the two instruments overlapping a short distance in the visible spectrum. A third instrument with a dense glass prism, giving greater dispersion in the visible spectrum than either of the other two, is also desirable.

One of the most dependable forms of microradiometer is the Rubens linear thermopile as modified by Coblentz. With the receivers blackened by the method of Coblentz it is almost perfectly nonselective. In order to be sufficiently sensitive for ultraviolet work it must be used with a very high sensitivity Thompson galvanometer. We have used this method throughout the past year and have found it quite reliable in spite

of its delicacy. It is therefore to be recommended for most of the work outlined here.

In the X- and gamma-ray region the type of measurements (intensity and spectral distribution of energy) is the same as for light, but the methods are somewhat different. The total radiation can be measured as with light by completely absorbing the radiation and measuring the heat developed, but this method involves very great experimental difficulties and is not reliable. Either photographic or ionization chamber methods are those generally used and are far preferable. It must be remembered, of course, that they are secondary methods, and proper allowance must be made for any spectral variations in sensitivity.

For spectral distribution of energy an X-ray spectrometer of the original Bragg form, with suitable ionization chamber and electroscope, will perhaps be as convenient as any, although photographic methods and other forms of spectrometers may also prove useful.

The radiation used on biological forms must be controlled largely by filters which can be standardized, when necessary, from the spectroradiometric equipment outlined above. This applies to the X-ray region as well as to light.

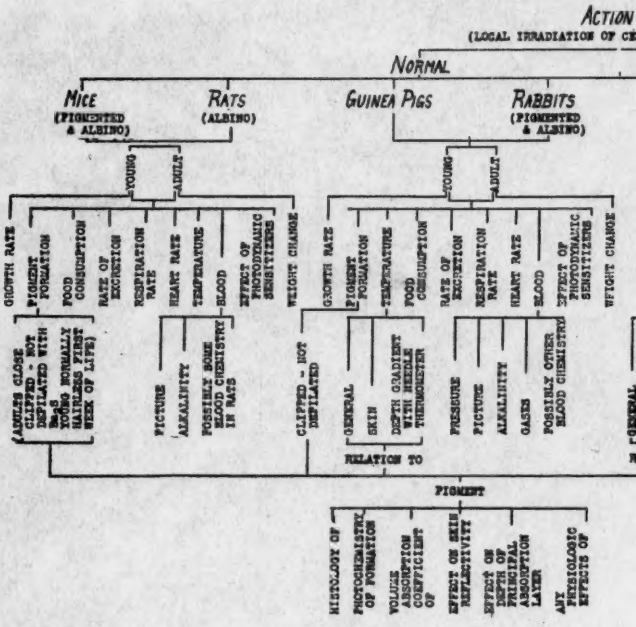
Only such radiation as is absorbed by an object can produce an effect on that object. This applies to all thermal, photochemical, and other physical phenomena involving a transfer of energy. In order that the amount of radiation absorbed at every wave-length may be known, the reflection coefficients and, if the object is at all transparent, the transmission coefficients must be determined throughout the whole radiation spectrum. Also, if a volume effect in a transparent object is involved, the absorption per unit distance travelled in the object must be measured. The methods here must be chosen or devised according to the particular kind of matter and of radiation under consideration, no one rule being adequate for all the work outlined.

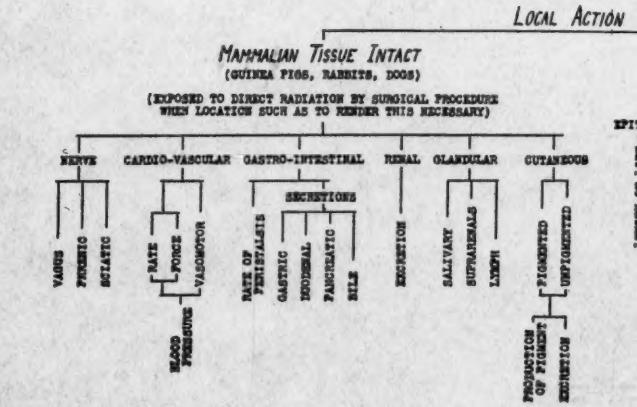
All the foregoing must be applied to all the research proposed in the accompanying outline in order that the optical conditions under which the work is done will be established beyond question. Further physical precautions to be taken can best be discussed when detailed protocols are prepared, covering the several physiological problems involved in this outline.

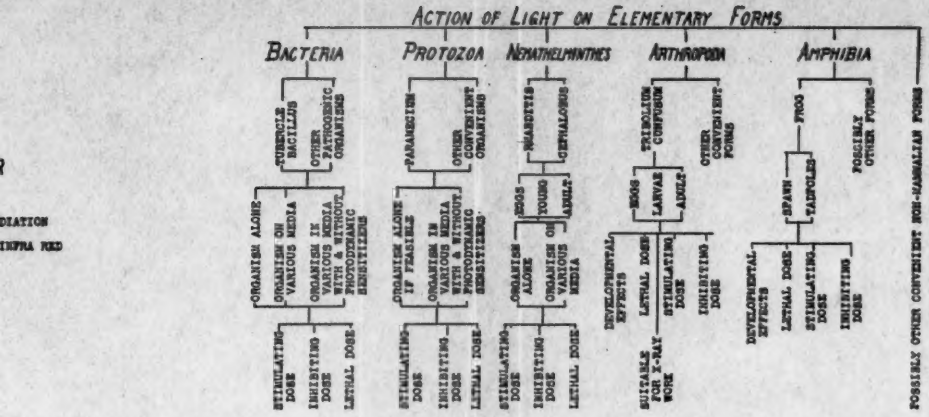
From recent work by Baly and Semmens at Liverpool and Morrison at Princeton, it appears that polarized light may act differently on certain organisms than unpolarized radiation. This may be of con-

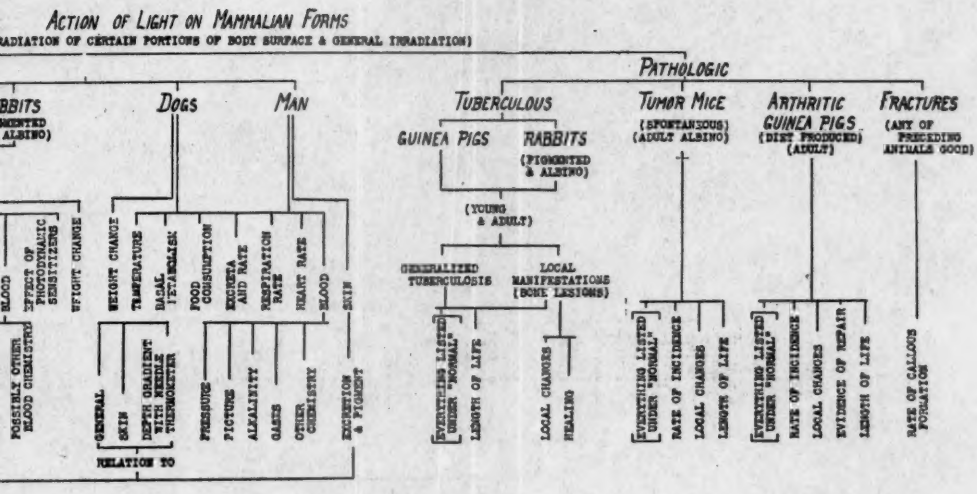
Outline of Proposed Research on the Action of Light on Living Matter

INVESTIGATION TO COVER, IN EVERY CASE, THE KNOWN RADIATION SPECTRUM FROM X-RADIATION THROUGH VISIBLE TO EXTREME INFRA RED






ACTION OF LIGHT ON ELEMENTARY FORMS
BACTERIA
PROTOZOA
NEMATHELMINTHES
ARTHROPODA
AMPHIBIA
TUBERCLE BACILLUS
OTHER PATHOGENIC ORGANISMS
PARAMECIUM
OTHER CONVENIENT ORGANISMS
NEMATODES
GEPHALOPODS
TRICHINA CONFUSA
OTHER CONVENIENT FORMS
FROG
SPAWN
TADPOLES
FOSSIBLY OTHER FORMS
EGGS
YOUNG
ADULT
LARVAE
ADULT
ORGANISM ALONE
ORGANISM ON VARIOUS MEDIA
ORGANISM IN VARIOUS MEDIA WITH & WITHOUT PHOTODYNAMIC SENSITIZERS
ORGANISM ALONE IF FEASIBLE
ORGANISM IN VARIOUS MEDIA WITH & WITHOUT PHOTODYNAMIC SENSITIZERS
ORGANISM ALONE
ORGANISM ON VARIOUS MEDIA
DEVELOPMENTAL EFFECTS
LETHAL DOSE
STIMULATING DOSE
INHIBITING DOSE
SUITABLE FOR X-RAY WORK
STIMULATING DOSE
INHIBITING DOSE
LETHAL DOSE
POSSIBLY OTHER CONVENIENT NON-MAMMALIAN FORMS


ACTION OF LIGHT ON MAMMALIAN FORMS
RADIATION OF CERTAIN PORTIONS OF BODY SURFACE & GENERAL IRRADIATION)
DOGS
MAN
PATHOLOGIC
TUBERCULOUS
GUINEA PIGS
RABBITS
(PIGMENTED & ALBINO)
(YOUNG & ADULT)
GENERALIZED TUBERCULOSIS
LOCAL MANIFESTATIONS (BONE LESIONS)
TUMOR MICE
(SPONTANEOUS) (ADULT ALBINO)
ARTHRITIC GUINEA PIGS
(DIET PRODUCED) (ADULT)
FRACTURES
(ANY OF PRECEDING ANIMALS GOOD)
WEIGHT CHANGE
TEMPERATURE
BASAL METABOLISM
FOOD CONSUMPTION
ESCHERICHIA AUD RATE
RESPIRATION RATE
HEART RATE
BLOOD
SKIN
GENERAL
SKIN
DEPTH GRADIENT WITH NEEDLE THERMOMETER
RELATION TO
PRESSURE
PICTURE
ALKALINITY
GASES
OTHER CHEMISTRY
EXCRETION & PIGMENT
EVERYTHING LISTED UNDER "NORMAL"
LENGTH OF LIFE
LOCAL CHANGES
HEALING
RATE OF INCIDENCE
EVIDENCE OF REPAIR
RATE OF CALLOUS FORMATION

PHYSIOLOGIC EFFECTS OF

CAL ACTION OF LIGHT ON VERTEBRATE TISSUE
TISSUE IN VITRO (SURVIVING)
(MAINTAINED IN VARIOUS SUITABLE MEDIA)
(EXPOSED TO DIRECT RADIATION)
EPITHELIUM
MUSCLE
SPECIAL ORGANS
BLOOD
LENGTH OF LIFE
PIGMENT CHANGE
SMOOTH
STRIPED
HEART (FROG, TURTLE)
POSSIBLY OTHERS
DURATION OF ACTION
RATE
FORCE
DURATION & DEGREE OF CONTRACTION
LACTIC ACID & OTHER PRODUCTS
ERYTHROCYTES
LEUCOCYTES
PLATELETS
CLOTTING
AGGLUTINATING POWER
CHANGE IN FORM
HAEMOGLOBIN CONTENT
HAEMOLYSIS
CHANGE IN FORM — ERYTHROBLASTS
COLOR INDEX — HAEMOGLOBIN
DEGREE
DURATION
PHAGOCYTIC ACTION
DEGREE
DURATION
MOTILITY
CHANGE IN FORM
FORMATION OF
DESTRUCTION OF
PREVENTION OF
DEGREE
TIME REQUIRED
ORGANISMS FOR WHICH PARTICULAR MUSCLE HAS BEEN DEVELOPED AGGLUTININS
OTHER ORGANISMS
CHANGES IN — ALKALINITY

siderable importance and warrants further investigation. At present not enough is known of these effects to justify the addition of polarized light to all parts of this program, but, in so far as elementary organisms are concerned, this addition might be desirable.

Polarized light is defined by the same quantities, total energy and spectral distribution of energy, as is unpolarized light, but in addition the extent and character of the polarization must be specified. A suitable compensator, preferably of the Babinet-Soleil type, together with some uncemented form of polarizing prism should be sufficient, with the above radiometric equipment, for these measurements.

It is realized that many changes in this scheme may be necessary as work progresses. Much of the material included here may prove unprofitable, and new experimental results will doubtless suggest further investigations, but it is hoped that this may be at least a starting point.

This programme is an outgrowth of the plan of the late Dr. John H. Pryor of Buffalo for comprehensive research in this direction.

The writer wishes to thank Dr. Albert H. Garvin of Buffalo who originally suggested that this outline be prepared and who has given valuable advice and criticism, Dr. Horace LoGrasso and the other members of the staff of the J. N. Adam Memorial Hospital who have made helpful suggestions, and Dr. R. Plato Schwartz of the University of Cincinnati who suggested a part of the arrangement followed and who largely prepared the section on *Mammalian Tissue Intact.*

THE NEWER CONCEPTION OF THE TUBERCULID

NORMAN TOBIAS[1]

HISTORICAL

The old conception of scrofulous diseases of the skin was considerably changed by the discovery of the tubercle bacillus. Previous to that event *tuberculosis cutis orificialis* and *tuberculosis ulcerosa* were considered to be the sole skin manifestations of tuberculosis. Four years later, however, Riehl and Paltauf (1) called attention to another type of lesion caused by the tubercle bacillus, namely, *tuberculosis verrucosa cutis*.

Scrofula was a common dermatological term in those days for any peculiar ulcerative or suppurative skin disease occurring in a strumous individual. Lupus was also frequently used to designate any spreading ulcer of the skin. What is now termed *lupus vulgaris* was formerly called *lupus exedens* or *noli me tangere*, a disease that Erasmus Wilson (2) believed was an expression of an hereditary syphilitic taint.

In the early part of the eighteenth century, Willan and Bateman segregated lupus vulgaris from this group, and accurately described the disease.

Such diseases as *lichen scrofulosorum*, *acne varioliformis*, *erythema induratum* and *lupus erythematosus* had long been suspected, upon purely clinical grounds, of having some connection with tuberculosis, but it remained for Hallopeau at the International Dermatological Congress in 1896 to attempt a classification of this group. In the same year Darier (3) coined the term *tuberculid* to describe a group of cases occasionally associated with tuberculosis and characterized by (a) a benign course, (b) a tendency to spontaneous cure, (c) wide and symmetrical distribution, (d) tendency to occur in successive crops without fever, and (e) a varied histological structure.

THE CLASSIFICATION OF CUTANEOUS TUBERCULOSIS

The true tuberculoses of the skin are all caused by the tubercle bacillus and, although clinically different, are all manifestations of the same

[1] Metropolitan Building, Saint Louis, Missouri.

process. The type of the lesion depends upon the strain of the bacillus, the type of tissue, the location of the lesion, and the factors of individual susceptibility and immunity. This group may be classified as follows:

1. *Tuberculosis ulcerosa*
2. *Tuberculosis verrucosa cutis*
3. *Scrofuloderma*
4. *Lupus vulgaris*

These diseases are all characterized by the presence of tubercle bacilli in the lesions and a typical tuberculous histological structure.

The so called paratuberculoses or tuberculids are sometimes associated with tuberculosis. Their real significance is as yet not quite understood, although experimental work in the last few years has thrown much light on the subject. Some of the cases appear to have a nontuberculous origin, because of the infrequency of a characteristic tuberculous histology, the rarity of positive bacillary findings, and the frequent occurrence of negative physical findings as far as tuberculosis is concerned. The following diseases have been tentatively classified under the heading of tuberculids:

1. *Papulo-necrotic types (including acnitis, folliclis and acne varioliformis)*
2. *Lichen scrofulosorum*
3. *Sarcoid*
4. *Erythema induratum of Bazin*

There is still another group of skin diseases in which tuberculosis is claimed to be a remote factor. This assumption, however, is not entirely justifiable, for when evidence of a tuberculous infection is found in these cases it can more easily be assumed to be a coincidence rather than an etiological factor. More likely these diseases are cutaneous reactions to various internal agents and include the following diseases:

1. *Lupus erythematosus*
2. *Parapsoriasis*
3. *Pityriasis rubra pilaris*
4. *Erythema nodosum*
5. *Lupus pernio*
6. *Angiokeratoma*

THE TUBERCULID OF TUBERCULOUS ORIGIN

Tuberculids are rarely observed in sanatoria and chest clinics but are occasionally encountered in children's hospitals and clinics. The fact

that the lesions are small, insignificant and usually seen in infants, accounts for their infrequent recognition.

Much (4) considers tuberculids an expression of active tuberculosis and of toxin oversensitiveness.

Fishberg (5) states that it is the consensus of opinion that tuberculids, lichen scrofulosorum, sarcoid and erythema induratum are manifestations of a reaction of skin hypersensitiveness in tuberculous individuals, brought about by the emboli of dead bacilli in the skin carried there by the blood and lymph stream.

Hempelmann (6), in a series of 130 cases of pulmonary tuberculosis in children under two, found tuberculids in 23 per cent. There was evidence of lung or tracheobronchial involvement in all but one of the positive cases. Leopold and Rosenstern's (7) findings agree with those of Hemplemann. In a study of 30 cases of tuberculosis in infants, they discovered that 40 per cent had tuberculids. They concluded that the finding of tuberculids in infants was positive evidence of a focus of infection.

Rist and Rolland (8) in 1914 performed a series of experiments to explain the pathogenesis of tuberculids. They studied the reaction of the skin of tuberculous guinea pigs to reinfection with large doses of tubercle bacilli. Special attention was paid to the histological aspect of the reinoculation lesions and the behavior of the tubercle bacilli in them. When the reinoculated guinea pig was under the influence of a preëxisting tuberculosis, the reinfection manifested itself always as an acute hemorrhagic inflammation with necrosis. The tubercle bacilli in these reinoculated lesions all died off in a short time. They advanced the theory that tuberculids are a local inflammatory reaction caused by the destruction of bacilli in the skin of an individual in whom a state of allergy exists.

NONTUBERCULOUS TUBERCULIDS

Guy (14) has recently shown that other factors may be responsible for the production of these lesions. In two cases in adults, studied by this investigator, there was present in each case evidence of a dilated stomach, general enteroptosis and colonic stasis. Tuberculin tests were negative. Among other microörganisms, Streptococcus viridans was isolated from the stools. Both patients got well from rest in bed and treatment directed to the gastrointestinal tract.

Experimentally, this observer injected cultures of a green streptococcus

intracutaneously in these two patients, and produced chronic, indolent inflammatory lesions leaving scars and suggesting papulonecrotic tuberculids. Thirty controls on healthy individuals proved to be negative. He concluded from these results that papulonecrotic tuberculids in certain cases are the result of the dissemination of feebly pathogenic microörganisms from different foci of infection, their localization and the type of lesion formation being determined by circulatory stasis and lowered resistance.

Strumia (10) has demonstrated that certain types of staphylococcus and streptococcus can produce lesions identical in all respects to *acne varioliformis*. In two cases studied by him the lesions were characterized by induration and woody edema, hemorrhagic deep necrosis and deep varioliform scarring.

He isolated Staphylococcus aureus and Streptococcus pyogenes from the nose and throat of one of these patients and the same microörganisms from the lesions themselves in both cases. Typical lesions of *acne varioliformis* were produced in one patient by the intracutaneous injection of stock and autogenous cultures of these bacteria. Fragments of the lesions, injected subcutaneously and intraperitoneally in two guinea pigs, produced no evidence of tuberculosis on autopsy, either macroscopically or microscopically. Strumia believes, on the basis of these results, that a definite tuberculous factor can be excluded in many of these cases.

Darier (11) classifies *erythema induratum*, or *Bazin's disease*, with the hypodermic tuberculids. The disease is a chronic, recurring disorder, usually involving the skin of the legs, especially the calves, and characterized by deeply situated nodules and ulcerations. Thibierge and Ravaut, Carle, Phillippson and Jadassohn, Fox, and others have proved conclusively that certain types are due to the tubercle bacillus, although the microörganism is found infrequently and the histology is not always characteristic.

As early as 1899, however, Galloway (12) ventured the opinion that there was more than one clinical type of erythema induratum and that different causes produced the different types of the disease. He classified the disease as follows: (1) The definitely tuberculous type, giving tuberculous reactions, positive animal inoculations and positive tuberculous findings in the physical examination. (2) The nontuberculous cases with negative physical findings and a non-characteristic histological picture. The giant cells which are occasionally present in this type are

usually of the irritation or foreign-body type. The blood-vessels in the lesions undergo changes suggesting obliterative endarteritis, resembling those of the specific granulomata.

Whitfield (13) in 1901 also distinguished two types of the disease. He found the majority of the nontuberculous cases in middle-aged women who suffered from some form of cardiac weakness. The lesions in these cases were more acute than the true tuberculous types and were more amenable to treatment.

Lesions resembling erythema induratum are occasionally caused by syphilis, and the clinical picture in these cases is difficult to differentiate from the true cases of the disease. In other cases vascular changes are more prominent, and form the connecting link between erythema induratum and the acute painful disease, erythema nodosum. Other cases are related to the group of lesions which Darier calls sarcoids. Whitmore (14) has recently described a case of type 3 sarcoid (erythema induratum type) of 4 years duration, in a white male, age 27, in which the physical findings for tuberculosis and syphilis were negative, but which cleared up following the removal of "cryptic" and friable tonsils and the treatment of a severe gingivitis. There was no recurrence after five years. The section showed marked perivasculitis and endovasculitis, but no necrosis or giant cells.

There is every reason to believe that Rist and Rolland's hypothesis can be applied to microörganisms other than the tubercle bacillus. The dissemination of bacteria in the blood of an individual having a focus of infection, and in whom a state of allergy already exists, may be the cause of various diseases, such as erythema multiforme, erythema nodosum, and certain types of purpura.

The rôle of septic infection in diseases of the skin has been brought out by Goeckerman (15) in his study of disseminated lupus erythematosus. He suggests that in this disease there is a "cross fire from tuberculosis and septic infection, the one creating an allergic background, while the other periodically excites explosions in the predisposed and unstable organism." Stokes, on the other hand, attempts to explain different reactions of the body to the tubercle bacilli in this manner: When the septic infection creates hypersensitiveness, the result of a hematogenous infection with tuberculosis is a tuberculid, while when tuberculosis creates hypersensitiveness, a streptococcus or septic invasion results in disseminated lupus erythematosus. Stokes (16) suggests the term *septids* to cover those cases of tuberculids that improve following the removal of a focus of infection.

Darier (17) has recently advocated the term *tuberculoid* to replace the word *tuberculid*, as first suggested by Barthelemy in 1896. This term would indicate the analogy and the possible relation of the condition without implying a tuberculous nature. Recent investigation has shown conclusively that the complete picture, clinically and histologically, can be produced by microörganisms other than the tubercle bacillus. One must conclude from these facts that the infections called tuberculids, although a clinical entity, have a variable etiology. A thorough physical and complete laboratory examination are necessary to discover the causative factors.

SUMMARY

1. Tuberculids may occur in individuals in whom no evidence of tuberculous infection can be discovered.

2. Lesions simulating tuberculids have been produced experimentally in cases in which the factor of active or latent tuberculosis was definitely excluded.

3. In some cases the lesions may be said to represent a cutaneous reaction on the part of an allergic skin to a focus of infection. In other cases they are the result of local infection of the skin, this condition being favored by lowered resistance and circulatory stasis.

4. In every case tubercle-bacillus infection should be first ruled out, but the rôle of other microörganisms must also be taken into consideration.

5. The term *tuberculoids*, advocated by Darier, appears to be a more appropriate designation for this condition.

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A CLINICAL STUDY OF SKIN HYPERSENSITIVENESS TO TUBERCULIN

PAUL M. ANDRUS[1]

For four and a half years we have employed tuberculin intracutaneously more or less as a routine measure. Having no clear-cut conception of the significance of the results as related to diagnosis or prognosis, it has seemed well to study their interrelation in the available material.

The study is based on an analysis of 1728 tests on an even 1000 adult admissions. The majority received tests shortly after admission, and many were tested at varying intervals during residence and at discharge. Of these admissions 58 were considered to have nonactive pulmonary tuberculosis and not to require treatment, 114 were diagnosed nontuberculous although the majority of them had chronic pulmonary or bronchial affections, and the remainder were considered to have active pulmonary tuberculosis and to be in need of treatment.

Technique: One-tenth of a milligram of O. T. (Parke, Davis and Co.) was used in 0.1 cc. volume. This dose was selected as rarely giving a constitutional reaction, and at the same time keeping the negative threshold higher than with the more commonly used 0.05 mgm. Injections were made on the anterior or lateral surface of the forearm with a fine platinum needle, avoiding the superficial veins. A well-marked wheal with sharply defined margins was the index of proper placing of the material. For some time control injections of the diluent were used. On no occasion were definite inflammatory phenomena observed, and controls were accordingly discontinued. Several cubic centimetres of tuberculin were pooled to ensure uniform strength of the stock over a period of time. Dilutions of 1 to 1000 were made monthly with 0.25 per cent phenol in normal physiological salt solution, and preserved in the ice-chest. Reactions were read at forty-eight hours and classified and recorded with measurements as follows:

Negative: No definite inflammation observed. Occasional localized discolorations only have been considered negative.

[1] Queen Alexandra Sanatorium, London, Ontario.

Weakly positive: Definite inflammation not in excess of 3 by 3 cm. Papule and areola of redness may or may not be separately distinguishable.

Moderately positive: Well-marked inflammation with separately distinguishable papule and areola of redness, the latter not in excess of 4 by 6 cm. but greater than described under weakly positive.

Strongly positive: Inflammation as under moderately positive but in excess of 4 by 6 cm.

Interpretations as above have however been altered on occasion by unusual severity of inflammation phenomena or special features, and thus thrown into a higher classification. Occasional constitutional reactions have been ignored, the study being purely one of local hypersensitiveness.

In using the above classification it must be appreciated that those reactions classed as weakly positive showed very definite inflammatory processes, and were in no sense doubtful reactions, that those classed as moderately positive showed well marked inflammatory features, and that the term strongly positive has meant reactions of unusual severity and might perhaps have been better classified as very strongly positive. Again, in the so called negative tests it must be realized that this means only that they failed to react to the arbitrary dose of 0.1 mgm. Different investigators have stated that tuberculous man and animals will always react to tuberculin if the dose be raised sufficiently high. Our negative tests should therefore be regarded only as indicating unusually low hypersensitiveness.

CLINICAL STUDIES

Since Krause (1) has stated that "the reacting capacity of the tissues (skin) of tuberculous man and animals is blunted by such events as the general reaction to tuberculin," and since the majority of our tuberculous patients are admitted in the febrile state, which in the absence of other demonstrable causes we presume to be a manifestation of the general tuberculin reaction, it has seemed advisable to look first into the correlation of these factors as bearing intimately on our further studies.

Tables 1 and 2 bear on this point. Table 1 illustrates the relation of local hypersensitiveness to the general tuberculin reaction. The results, it will be noted, are roughly similar whether or not the general tuber-

culin reaction (as evidenced by fever) is present, consisting of negative reactions to 0.1 mgm. of O. T. in 22 to 26 per cent of cases. These figures are, of course, quite relative and depend on our individual conception of what constitutes a low or blunted skin response. Thus, if we include also the weakly positive reactions in this category, the figures would be around 50 per cent which is still not characteristic. Again, if the general tuberculin reactions tend to induce lowered skin response, one would perhaps expect the latter to increase as the former diminishes. That such is not the case in the present series is seen in table 2. For this tabulation tests were performed on admission, and

TABLE 1

Correlation of tuberculin skin hypersensitiveness with the general tuberculin reaction (fever)

ACTIVE TUBERCULOSIS ON ADMISSION	FEVER PRESENT		FEVER ABSENT	
	number	*per cent*	*number*	*per cent*
Reactions negative to 0.1 mgm. O.T.	120	22	64	26
Reactions positive to 0.1 mgm O.T.	416	78	179	74
Total	536		243	

TABLE 2

Changes in tuberculin skin hypersensitiveness after four to six weeks' bed rest

ACTIVE TUBERCULOSIS ON ADMISSION	FEVER ON ADMISSION SUBSIDING		NO FEVER	
	number	*per cent*	*number*	*per cent*
Skin reactions stationary	79	60	40	48
Skin reactions increased	29	22	28	33
Skin reactions diminished	23	18	16	19
Total	131		84	

again after four to six weeks' rest treatment, during which time the fever subsided together with general improvement. Thus it will be seen that after such a period, local tuberculin hypersensitiveness remained stationary in 60 per cent of cases, increased in intensity in 22 per cent and diminished in the remainder. Again these changes were roughly similar after such a period of rest, whether or not initial fever (general tuberculin reaction) was present. The individuals shown in table 1 as having active tuberculosis but no fever had, in each case, symptoms or findings attributable to tuberculous lesions, such as recent haemorrhage or pleurisy, anatomic spread or marked disabilities, etc.

In table 3 is seen the relation of tuberculin skin hypersensitiveness to diagnosis and tuberculous activity. No essential differences are seen between the active and nonactive tuberculous groups. The nontuberculous group however shows a decided preponderance of negative reactions over the tuberculous, and a corresponding decrease in the positive reactions being most marked in the more strongly positive

TABLE 3

Correlation of tuberculin skin hypersensitiveness with diagnosis and activity

SKIN RESPONSE TO 0.1 MGM. O.T.	ACTIVE TUBERCULOSIS		NONACTIVE TUBERCULOSIS		NONTUBERCULOUS	
	number	*per cent*	*number*	*per cent*	*number*	*per cent*
Negative	187	24 } 57	12	21 } 55	49	43 } 75
Weak	256	33 }	20	34 }	36	32 }
Moderate	230	30 } 43	19	33 } 45	24	21 } 25
Strong	106	13 }	7	12 }	5	4 }
Total	779		58		114	

TABLE 4

Correlation of tuberculin skin hypersensitiveness with degree of tuberculous involvement

SKIN RESPONSE TO 0.1 MGM. O.T.	MINIMAL		MODERATE		ADVANCED	
	number	*per cent*	*number*	*per cent*	*number*	*per cen*
Negative	41	17 } 44	72	23 } 55	66	29 } 66
Weak	66	27 }	100	32 }	86	37 }
Moderate	79	33 } 56	100	32 } 45	53	23 } 34
Strong	55	23 }	36	13 }	25	11 }
Total	241		308		230	

groups. Thus, in diagnostic problems which would naturally occur largely among the minimal group, negative reactions occurred in 17 per cent of cases (table 4) as against 43 per cent in the nontuberculous (table 3). In the absence of definite lesions it would then appear that a failure of response to 0.1 mgm. O.T. favors a nontuberculous diagnosis in the proportion of 43 to 17, or 5 to 2. Similarly (tables 3 and 4), a well-marked skin reaction (moderate or strong) to 0.1 mgm. O.T.

favors a diagnosis of tuberculosis in the proportion of 56 to 25, or better than two to one.

Again, skin allergy has been correlated with extent of tuberculous involvement (American Sanatorium Association). The classifications refer to anatomic involvement only, and do not take cognizance of the degree of sickness, although all were clinically ill. The outstanding features of this study would seem to be a progressive increase in the number of weaker skin reactions with the more advanced lesions, and a corresponding predominance of the more marked reactions in the earlier cases.

In tables 5 and 6 tuberculin skin hypersensitiveness has been correlated with clinical progress. In table 5 is seen the relation of degree of hypersensitiveness on admission to subsequent progress. The findings, it will be noted, are not unlike those under extent of involvement. Thus, the retrogressing cases (naturally the more advanced anatomically) show a predominance of the weaker reactions, while the improving group (containing the majority of those with minimal lesions) have relatively more well marked skin reactions. A review also of 48 individuals who died within a year of the test (not shown in tables) showed similar but more pronounced findings, 45 per cent having negative reactions and only 3 per cent strongly positive reactions.

In table 6 are detailed the changes which occurred in tuberculin skin hypersensitiveness over a period of time. The material for this study consisted of individuals who had repeated tests over months to years during the course of treatment. Inasmuch as retrogressive cases are confined to bed, serial tests were not performed to any extent on this class, and those in the first section of table 6 represent only improving cases. The second section of table 6 represents individuals who were tested at the time of discharge from the institution as quiescent or better, and again on readmission after relapse. From this table it will be seen that of improving tuberculous individuals about 50 per cent maintained their skin allergy at constant level during treatment, while in the remainder skin allergy increased and diminished about equally. These figures, it will be noted, approximate those occurring after the initial few weeks of rest and improvement (see table 4). As a matter of fact, although we have for obvious reasons refrained from further complicating our tables, the changes in skin hypersensitiveness occurred for the most part during this initial rest period, and remained roughly stationary during the subsequent months or years of treatment. Sixty-

two per cent of those having repeated tests showed their allergic level to be stationary after the initial changes had occurred. The next most common variation was an initial increase of hypersensitiveness with subsequent fall: this class comprised 22 per cent. Some, of course, gave erratic rises and falls without apparent accompanying clinical changes. Such courses were however not a conspicuous feature, and the constancy of type of reaction over long periods of time was rather

TABLE 5

Correlation of tuberculin skin hypersensitiveness with subsequent progress under treatment

SKIN RESPONSE TO 0.1 MGM. O.T. ON ADMISSION	IMPROVED ON TREATMENT		RETROGRESSED ON TREATMENT	
	number	*per cent*	*number*	*per cent*
Negative	140	21 } 52	43	37 } 74
Weak	206	31	43	37
Moderate	222	33 } 48	22	19 } 26
Strong	95	15	8	7
Total	663		116	

TABLE 6

Correlation of changes in tuberculin skin hypersensitiveness with progress in the tuberculous

REPEATED TESTS SHOW SKIN HYPERSENSITIVENESS	IMPROVING UNDER TREATMENT		RELAPSING AFTER TREATMENT	
	number	*per cent*	*number*	*per cent*
Stationary	284	47	52	36
Increasing	160	28	72	50
Diminishing	154	25	24	14
Total	598		148	

surprising. The cases that relapsed however behaved somewhat differently, in that 50 per cent showed an increase of skin hypersensitiveness at the time of relapse above their previous level, while smaller numbers showed stationary or decreased hypersensitiveness.

Lastly, the nutrition of the patient, and the presence or otherwise of tuberculo-complement fixation, have been correlated with the degree of skin allergy in a limited number of cases. The results are as seen in tables 7 and 8.

The correlation with nutrition was suggested by the reports of other

investigators that poorly-nourished tuberculous guinea pigs showed less marked skin reactions than did well-nourished animals. This has not been confirmed for man in the present series, in that the well-nourished individuals showed a preponderance of weak and negative reactions, and the poorly-nourished relatively more well-marked reactions. One would rather expect the well-nourished individuals to represent the

TABLE 7

Correlation of tuberculin skin hypersensitiveness with nutrition

SKIN RESPONSE TO 0.1 MGM. O.T.	NUTRITION GOOD		NUTRITION POOR	
	number	*per cent*	*number*	*per cent*
Negative	42	33 } 63	66	23 } 57
Weak	38	30	98	34
Moderate	38	30 } 37	86	29 } 43
Strong	8	7	42	14
Total	126		292	

TABLE 8

Correlation of tuberculin skin hypersensitiveness with tuberculo-complement fixation

SKIN RESPONSE TO 0.1 MGM. O.T.	FIXATION POSITIVE		FIXATION NEGATIVE	
	number	*per cent*	*number*	*per cent*
Negative	84	26 } 58	62	30 } 63
Weak	106	32	68	33
Moderate	74	23 } 42	60	30 } 37
Strong	64	19	14	7
Total	328		204	

minimal and more favorable types of lesions and to show correspondingly stronger reactions. The differences are however not pronounced.

The presence or absence of tuberculo-complement fixation appears to bear no remarkable relation to the degree of skin allergy. The less marked reactions are slightly in excess in those showing tuberculo-complement fixation, and *vice versa* in those without tuberculo-complement fixation. This is perhaps what one might expect, in that tuber-

culo-complement fixation has in this institution (2) shown a tendency to accompany the more advanced and less favorable types of tuberculosis. Other investigators have also been unable to demonstrate any material relation between these reactions.

SUMMARY AND CONCLUSION

1. In the series of adult tuberculosis studied, the presence of the general tuberculin reaction (as indicated by fever) has no constant bearing on the degree of tuberculin skin hypersensitiveness.

2. The degree of tuberculin skin hypersensitiveness offers no clue to differentiate active from nonactive pulmonary tuberculosis in a clinical way.

3. In the absence of definite tuberculous involvement, negative tuberculin skin tests (as herein defined), would tend to throw the balance of evidence in favor of a nontuberculous diagnosis.

4. In tuberculosis diagnostic problems the presence of well-marked tuberculin skin reactions would tend to throw the balance of evidence in favor of a tuberculous diagnosis.

5. The earlier and more favorable types of tuberculosis tend to the higher levels of tuberculin skin hypersensitiveness, and the more advanced and less favorable types to the lower levels.

6. No characteristic changes in degree of tuberculin skin hypersensitiveness occur during the favorable progress of tuberculous disease. Changes occur one way or the other in about 40 per cent of cases relatively early and then tend to maintain a constant level.

7. The level of tuberculin skin hypersensitiveness rises in 50 per cent of tuberculous individuals at the time of relapse.

8. The data as offered by degree of, or changes in, tuberculin skin hypersensitiveness is of small practical value in the clinical estimation of a given case.

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A NOTE ON DREYER'S ANTIGEN[1]

CHARLES H. BOISSEVAIN

Some observations made last year on the *defatted B. tuberculosis antigen* of Dreyer are here briefly reported.

The antigen was prepared according to Dreyer's directions (1) from a stock laboratory strain of human tubercle bacilli. This strain was recovered in 1921 from a case of genitourinary tuberculosis, and has since been cultivated on glycerin-agar.

Ten guinea pigs of about 500 gm. each were inoculated subcutaneously in the left groin with 0.2 cc. of an emulsion of live bacilli from the same strain, containing about 100 million bacilli per cubic centimetre. Five of the animals were kept as controls. The other five were treated with the antigen in the manner prescribed by Dreyer. Injections were given once a week, beginning five weeks after inoculation, and the dosage was controlled according to the weight curve. When loss of weight occurred, the injections were reduced or omitted.

Most of the animals in both series gained weight at first, and afterward lost progressively. One control died one week after inoculation. It showed no tuberculous lesions. The other controls died of general tuberculosis after 120, 105, 91, and 136 days (an average of 113 days).

The treated animals died of generalized tuberculosis after 136, 104, 117, 117, and 55 days (average 95 days). It should be noted that the strain of tubercle bacilli used was a virulent one, while Dreyer worked with relatively avirulent strains. Our observations do not justify any inferences regarding the effect of the antigen on chronic experimental tuberculosis.

Two patients with far-advanced pulmonary tuberculosis have, at their own request, been treated with the same antigen by Dr. G. B. Gilbert. The treatment, continued now for about eight months, has not shown any notable effects, either favorable or unfavorable.

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[1] From the laboratories of the Colorado Foundation for Research in Tuberculosis, Colorado Springs, Colorado.

THE TUBERCULO-COMPLEMENT-FIXATION AND INHIBITIVE TESTS

RESULTS OBTAINED BY REPEATED TESTS IN CLINICAL NORMALS, TUBERCULOSIS CONTACTS, AND 1000 CASES[1]

A. H. W. CAULFEILD

IN COLLABORATION WITH

W. R. HODGE, M. F. MacLENNAN, FLORENCE LaRUSH, W. E. OGDEN, HORACE MacINTYRE, G. C. ANGLIN AND CECILE COHEN

Introduction

A. H. W. CAULFEILD

The purpose of these papers is to demonstrate the clinical value which can be attached to the inhibitive and tuberculo-complement-fixation reactions, either during the investigation for diagnosis or throughout the medical direction necessary for patients who are either positively tuberculous or suspected of being such.

The clinical material on which they are based is from the Toronto chest clinic of the Department of Soldiers' Civil Reëstablishment. The character of this clinic is somewhat unusual, especially in its control over the patients and the opportunity for long-continued observation. It is felt that these circumstances and the many facilities available for all examinations have enabled us to estimate the value of these tests to a remarkable degree.

In many instances the ex-soldier's history of chest symptoms shows a mixture of strain, exposure, etc., together with the early application of rest, that is, hospitalization, which again may be periodic in character. There is frequently a distinct disability with a varied symptomatology and past history suggestive yet not typical of tuberculosis. The purpose of the Department in establishing this clinic was to afford every facility for diagnosis, for the periodic evaluation of any disability or working capacity (on which the pension would be based) and for med-

[1] From the Toronto Chest Clinic of the Department of Soldiers Civil Reëstablishment, and the Research Division of the Connaught Laboratories of the University of Toronto.

ical advice or treatment of the patient. These combined objects gave the clinic an opportunity for following, in a continuous manner, the course of the disease in a large number of patients.

Reëxamination is required every six months for pension purposes, or more frequently if this seems advisable on medical grounds. Periodic reports by the nursing social service on home conditions, rest, exercise, change in symptoms, etc., are filed in the history and are before the clinician for the revisional examinations at the clinic. For obvious reasons an investigating social service is available for reports on the degree and kind of work done, as certified by the patient's employer. Observation beds adjoining the clinic, and looked after by the clinic staff, are available for cases in which this is considered desirable either for diagnosis or a fuller estimation of the patient's condition at any time.

The manner in which the radiological work has been carried out has altered during the existence of the clinic. In the first two years the stereoscopic plates were independently reported upon by Dr. G. E. Richards (Director of the Department of Radiology, Toronto General Hospital), this report subsequently being utilized for guidance by the clinician in reading his plates, and for inclusion in his report upon the case. Since then the plates have been sent direct to the clinic, interpreted by the clinician, and only referred to Dr. Richards when seemingly advisable.

The need for accuracy in diagnosis and in the periodic evaluation of the disability in the pensioners, together with the many difficulties to be encountered in both problems, was sufficient for the Department to acquiesce in the establishment of a laboratory division, more or less research in character, of the clinic. This has been accomplished by means of arrangements between the Department of Soldiers' Civil Reëstablishment and the Research Division of the Connaught Laboratories of the University of Toronto. While various other investigations have been attempted and are still under way, the inhibitive and tuberculo-complement-fixation[2] reactions have been carried out as a routine measure at the clinic examinations since the spring of 1919. Until January, 1922, these two reactions were under the immediate direction of Dr. W. R. Hodge. In this manner the serological work has been as free as possible from any influence which I might otherwise have brought to bear upon it, because of my previous experience with and

[2] Hereinafter abbreviated to *t.c.f.* reaction.

interpretation[3] of the two tests. The large number of tests made it necessary to card-index and otherwise adopt such laboratory methods which would do away with the possibility of bias in the report on any serum tested.

With increase in attendance at the clinic the number of my colleagues had to be rapidly increased to cope with the number of patients. With one exception those who were appointed were either antagonistic to, or skeptical of, the value of serological data, any experience with which had been obtained with the results of the *t.c.f.* reaction alone. All had previously had practical experience in both sanatoria and tuberculosis clinics. All have been converted by observing the routine serological results and their relationship to the continuous medical histories carried on the cases. My influence in this, I believe, ceased with the suggestions made on the manner in which the combined serological tests should be interpreted. The continuous supervision of these cases compels one to face periodically the data recorded, and the typed diagnosis, classification, prognosis, etc., made after each examination—not only those made by oneself but also those by one's colleagues.

The total attendance since 1919 has varied each year between 6,000 and 8,000; many of these, however, represent reëxaminations of the same patient. The number of sera tested (both tests) was over 13,000 by January, 1924.

The literature on the tuberculo-complement-fixation (*t.c.f.*) reaction is sufficient to render unnecessary any introduction, even though its exact significance as regards clinical interpretation may still be controversial. The inhibitive reaction, however, is in a sufficiently different category, so that a few explanatory remarks would seem to be expedient.

In 1910 (1), while experimenting with the *t.c.f.* reaction, particularly to determine, if possible, why the reaction was absent in a percentage of all types of the definitely tuberculous, a technique (2) was evolved, which, with minor modifications, is identical with that used in the present series of observations. Although the test brings together a particular[4] type of tuberculo-antigen, the inactivated serum to be tested, complement, and, after an interval, sensitized corpuscles, the

[3] This might be summarized by an opinion (1909) that the *t.c.f.* reaction would not be a satisfactory means of diagnosis and subsequent claims for the inhibitive reaction that the results are of distinct clinical value.

[4] Largely if not entirely lipoidal. The original technique is given in reference (2).

anticomplementary strengths of the antigen used bar it from being regarded as a modification of the *t.c.f.* reaction.

As experimentation failed to give me any satisfactory or fundamental explanation of the cause of the varying end results with different sera, I hesitated to name the phenomenon ((*1*) *p. 128*) a definite reaction comparable to such serological tests as complement fixation, agglutination, etc. Finally, for convenience I suggested the term *inhibitive reaction,* and for descriptive purposes accepted the degree of reaction, that is, the amount of haemolysis, as indicative of the amount of *inhibitin* present in the serum. Possibly the reaction itself had better been termed *inhibitin.*

The test is done by adding serum to three multiple dilutions of tuberculo-lipoidal antigen (accurately titrated as to anticomplimentary strength), and the end results show as degrees of haemolysis or no haemolysis. As a convenient conception, one can look upon the end results as indicating the extent to which a particular serum "digests" this antigen, the degree of "digestion" being shown by the extent to which the anticomplementary strength of the antigen is destroyed. Although the antigen is largely if not entirely lipoidal in character, it is legitimate, until disproved, to regard the end results as showing degrees of interaction between this type of antigen and the serum tested.

The degrees of end reactions have unfortunately from that time on been given different designations, by utilizing either the letter *a* or the numeral *1* to signify marked degrees of haemolysis. In this series they are labelled as first, second and third-class, and negative. First and second-class results signify very complete haemolysis, as did the former nomenclature of *a* or *1.* Third-class means slight, and negative no greater haemolysis than would be obtained with saline solution (replacing serum) to the different strengths of antigen used. Negative and third-class results are elsewhere grouped together in the following papers as *normal;* and second and first-class results as *positive.*

It is convenient to group the degrees of the end results of the test into two classes for the preparation of statistical tables. The term *normal* is appropriate in that either a negative or, more frequently, a third-class result is the usual finding among the *normal.* It is misleading in the implied suggestion that it should not be obtained in the clinically tuberculous; whereas it can be expected in many phases throughout the course of the disease, and when so obtained can reason-

ably be regarded as confirmatory of the clinical estimation of the case. The term *positive* for either a first or second-class result is entirely satisfactory in that, as we interpret the test, it signifies the presence within the host of the tubercle bacillus.

Calmette (3), shortly before the original publication on the inhibitive reaction, reported a reaction which he termed *inhibiteur:* this was demonstrated by adding a second serum to an antigen plus fixation-serum mixture. The *inhibiteur* reaction was positive when the addition of the second serum prevented the fixation which would otherwise have taken place, that is, haemolysis instead of no haemolysis as an end result. This technique can legitimately be regarded as a modification of the complement-fixation reaction. In a recent publication Hodge and MacLennan (4) have brought forward two important types of evidence that the substances in the serum responsible for the *inhibitive* and for Calmette's *inhibiteur* reaction are probably identical. Calmette's samples of *inhibiteur* sera were obtained from *hyperimmunized cows:* subsequent publications stated that it is only rarely obtained with human sera.

The clinical significance (5), (6), (7), (8), which can so frequently be attached to the results of the inhibitive reaction, has stimulated me to persist in its employment. In general, the positive results (first or second-class) are associated with clinical activity and a favorable prognosis. This has been demonstrated so frequently, and in cases in which on no other grounds would such an outcome have been prognosticated, that one is impelled to construe the appearance of a positive result as associated with bacterial activity and some phase of the immunological mechanism of the host. Cases are of course encountered in which no evidence of clinical activity is obtained, yet which give a positive test.

To illustrate the favorable aspect which positive inhibitive reactions lend to the prognosis, many of the group reported (1) (7) upon as initially giving this in marked degree in the years 1909 and 1910 are alive and working to-day. As examples, a case (*no. 123*) then suspected pulmonary and lymph-node tuberculosis, and a case (*no. 311*) then classified as far advanced, are to-day alive and working. The radiographic findings now show, respectively, a minimal and a far-advanced lesion.

With the antigen for the inhibitive reaction a *t.c.f.* reaction can occasionally (in from 2 to 3 per cent of the tuberculous) be demonstrated. The antigen must of course be diluted to an anticomplementary strength

of from $\frac{1}{4}$ to $\frac{1}{8}$ of a unit. All cases giving this infrequently found fixation have been dead many years. It was with this antigen only that the statement was made by me regarding the unfavorable prognostic value of a positive *t.c.f.* reaction. It is found so seldom that its use has been discontinued.

With each sample of serum tested for the *t.c.f.* and inhibitive reactions, a control Wassermann test (9) has been made. The number of sera which gave a positive Wassermann and a negative *t.c.f* reaction has been sufficient to make it difficult to estimate the rôle of the Wassermann "antibodies" when both tests were positive, whether the case were frankly tuberculous or not.

The Technique of the Complement-Fixation and Inhibitive Tests

W. R. HODGE, M. F. MacLENNAN AND FLORENCE LaRUSH

While various minor modifications have been tried from time to time, some to be retained and others discarded, the following has been the routine procedure for some time. Similar results will be obtained by any serological technique which meets the fundamental requirements of exact titrations and the necessary controls.

With both tests the so called micro-method has been used, that is, the serum to be tested is diluted to 1 in 10, and correlative amounts of the other ingredients are employed. The haemolytic system has been guinea-pig complement, sheep's corpuscles, and anti-sheep rabbit serum for haemolysin. The sera to be tested are inactivated in the usual way by immersion in a water-bath for half an hour at 56°C.

The antigen for the *t.c.f.* reaction has usually been Petroff's (12). Other antigens[5] have been tried from time to time, but the results reported have in almost all instances been obtained with this "extract."

Complement is titrated to determine the dilution representing 1 unit as follows:

1. Antigen control tubes:	*1*	*2*	*3*	*4*	*5*	*6*
Complement	0.1 cc. (1:50)	0.1 cc. (1:60)	0.1 cc. (1:70)	0.1 cc. (1.80)	0.1 cc. (1:90)	0.1 cc. (1:100)
Antigen (1:200)	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.
Saline solution (0.9%)	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.

[5] Other antigens were tested by "trying" them with sera selected from (1) those positive clinical cases which previously had given negative or close to negative results in the past, (2) sera from the students who had previously given some degree of fixation, and (3) anti-diphtheritic horse serum giving positive fixation with Petroff's antigen.

2. Saline control tubes:	*1*	*2*	*3*	*4*	*5*	*6*
Complement	0.1 cc. (1:50)	0.1 cc. (1:60)	0.1 cc. (1:70)	0.1 cc. (1:80)	0.1 cc. (1:90)	0.1 cc. (1:100)
Saline solution	0.2 cc.	0.2 cc.	0.2 cc.	0.2 cc.	0.2 cc.	0.2 cc.

The rack is placed in the ice-chest for one hour; in the water-bath at 37.5°C. for one-half hour; 0.1 cc. of the mixture is then added to each tube; incubated 15 minutes longer and readings taken.

Unit of complement: The dilution of complement in the antigen control tube showing almost complete haemolysis (or the dilution between that and the next weaker dilution) is considered as one unit. The antigen (1:200) will be slightly anticomplementary. Thus, if there is complete haemolysis in the saline solution control tube with 1:70 dilution of complement, there will be only *ACH*[6] in the antigen control tube having the same dilution of complement.

Mixture: This is a 3 per cent suspension of sheep cells, which have been centrifugated 15 minutes after the final washing, plus an equal volume of haemolysin. The mixture should be prepared as soon as the titration has been set up, and kept in the ice-chest: 0.1 cc. should contain $2\frac{1}{2}$ units of haemolysin.

Example of titration for complement-fixation test

Complement:	*1:50*	*1:60*	*1:70*	*1:80*	*1:90*	*1:100*
Antigen (1:200)	CH	CH	ACH	PH	PH	PH
Saline solution control	CH	CH	CH	ACH	PH	PH

1 unit of complement in this case would be 1:70 or 1:75.

Example of t.c.f. test

Tubes for each serum:	*1*	*2*	*3*	*4*
Serum (1:10)	0.1	0.1	0.1	0.2
Antigen (1:200)	0.1	0.1	0.1	
Complement	(2 units)	($2\frac{1}{2}$)	(3)	(2)

With each test three antigen control tubes, with 0.1 cc. of antigen and 2, $2\frac{1}{2}$ and 3 units of complement, respectively, and one antigen control tube with 0.2 cc. antigen and 2 units of complement are used. Racks are placed in the ice-chest overnight. In the morning 0.1 cc. of mixture is added to each tube. After this the racks are incubated in the water-bath at 37.5°C. Readings are taken when controls (1) for sera and (2) for antigen, containing 0.1 cc., are completely haemo-

[6] See abbreviations.

lyzed, and (3) the control for antigen containing 0.2 cc. is almost completely haemolyzed. Several negative and positive sera repeated from the last day's test, which have shown the same reaction in several previous tests, also serve to indicate the proper length of final incubation. Abbreviations and interpretation of readings as they are reported to the clinic are as follows:

CH = complete haemolysis; *ACH* = almost complete haemolysis; *PH* = partial haemolysis; *NH* = no haemolysis. The number 4 = no haemolysis; the number 0 = complete haemolysis; and the intervening numbers varying degrees of haemolysis.

CH to ±000 = negative
1000 to 1 000 = doubtful
2000 to 2±00 = very weak positive
3000 to 3±00 = weak positive
4000 to 4430 = positive
4440 = strong positive

The inhibitive test: The sera to be tested are inactivated and diluted 1 to 10 as for the *t.c.f.* reaction, but have as well any natural anti-sheep-corpuscle haemolysin absorbed before dilution. This is done by adding at least four drops of undiluted sheep cells to about 0.6 cc. of each serum, maintaining this contact for 20 minutes, centrifugating for 10 minutes and then pipetting off the clear, treated serum. This treatment with sheep corpuscles should immediately precede the test.

Antigen: (Alcohol-ether extract): 2 gm. of dried tubercle bacilli are extracted in 100 cc. alcohol-ether (50 cc. of each) by keeping it in a glass-stoppered bottle in a dark place, and shaking every day for two or three weeks. The alcohol should be absolute, and ether free from water. The clear extract is pipetted into an evaporating dish, evaporated in the incubator, sediment (left after evaporation) resuspended by warming the evaporating dish in the water-bath at 56°C., and rinsing it into a small, glass-stoppered bottle with sufficient alcohol-ether to make a 2 per cent solution, then filtered. The antigen should be kept in a dark place, and a fresh one made every two or three weeks. The tubercle bacilli used are grown in flasks of 5 per cent glycerine broth 4 to 6 weeks, killed by heating in an Arnold sterilizer, filtered, washed, and dried in an incubator at 37.5°C.

Titration to determine the anticomplementary strength of a new antigen: The antigen is diluted in the ratio of $1:\frac{1}{2}:\frac{1}{4}$, and titrated with varying dilutions of complement, as follows (0.1 cc. of required dilution of com-

plement being used in each tube, and 0.1 cc. of saline solution in place of serum):

Complement:	*1/10*	*1/20*	*1/30*	*1/40*	*1/50*	*1/60*	*1/70*	*1/80*	*1/90*
AE antigen 1/40	0.1	0.1	0.1	0.1					
AE antigen 1/80	0.1	0.1	0.1	0.1					
AE antigen 1/160	0.1	0.1	0.1	0.1					
Saline solution[7] (control tubes to determine one unit of complement)					0.2	0.2	0.2	0.2	0.2

The rack is placed in the water-bath at 37.5°C. for one hour; 0.1 cc. of haemolytic[8] mixture is added to each tube; incubated one-half hour longer, and readings taken.

The strength of complement used in the test should be about $2\frac{1}{2}$ units, or slightly more than two units (as determined by saline-solution control tubes). The antigen should be of such strength that with the weakest dilution there will be partial haemolysis in the tube containing about $2\frac{1}{2}$ units of complement. The desired relationship between strengths of antigen and complement is shown by the following titration results, in which complement dilution 1/30 contains $2\frac{1}{3}$ units:

Complement:	*1/10*	*1/20*	*1/30*	*1/40*	*1/50*	*1/60*	*1/70*	*1/80*	*1/90*
AE antigen 1/40	NH	NH	NH	NH					
AE antigen 1/80	ACH	PH	NH	NH					
AE antigen 1/160	CH	ACH	PH	NH					
Saline solution (control tubes to determine one unit of complement)					CH	CH	CH	ACH	PH

In this case dilution of complement 1/30 would be used in the test.

Example of inhibitive test

Tubes for each serum:	*1*		*2*		*3*		*4*
Serum (1:10)	0.1		0.1		0.1		0.2
Antigen	0.1	(1/40)	0.1	(1/80)	0.1	(1/160)	—
Complement	0.1		0.1		0.1		0.1

There should also be a control tube for each dilution of antigen, with 0.1 cc. saline solution in place of serum. (Antigen dilution 1/40, 1/80, 1/160 are mentioned simply to illustrate the ratio between the different strengths used, and, in order to retain this ratio, it will be found necessary to vary these dilutions according to the strength of the particular antigen being tested.)

[7] The saline solution used in this test is buffered with sodium and potassium phosphate to a pH of 7.0, as it has been found to give more consistent results than the unbuffered solution.

[8] The same sheep-corpuscle and haemolysin mixture as used with the *t.c.f.* reaction.

The racks are placed in the water-bath at 37.5°C. for one hour, 0.1 cc. of mixture is added to each tube and the racks replaced in the water-bath until there is partial haemolysis in the antigen control tube containing the weakest dilution of the antigen. The time required may exceed the half-hour allowed in the preliminary titration, as the antigen dilutions gradually become more anticomplementary during the time which elapses between the preliminary titration and the actual test.

Readings may be taken at once or after the racks have stood in the ice-chest over night.

The following interpretations would apply to an average test, but should be modified if the antigen proves to be stronger or weaker than was indicated by the preliminary titration:

4430[9]–4440	negative	Termed *normal* in other parts of these reports
4300–4420	third-class	
4200	third-class plus	
4100	second-class minus	Termed *positive* in other parts of these reports
4000	second-class	
3000	second-class plus	
2000	first-class minus	
CH –1000	first-class	

Groups of Cases Selected from 1000 Patients on Whom Serial Tests Were Done as a Routine Measure

A. H. W. CAULFEILD, W. E. OGDEN, HORACE MacINTYRE AND G. C. ANGLIN

The 1000 cases used in this report were obtained by drawing the histories alphabetically; these were summarized according to a definite questionnaire, and from these sheets the tables and percentages were compiled. The completion of the initial summaries took a good deal of time, so that the number of tests done since then has very materially increased. At the present time it is not unusual to find from 10 to 15 tests per case.

In table 1 are shown the percentage results obtained with the two serological tests in (1) cases in which an undoubted parenchymatous lesion was demonstrated by stereoscopic plates, (2) cases which were diagnosed clinically as nontuberculous, and (3) clinical normals.

These groups were selected as most suitable for demonstrating the differences which should be obtained with the two tests if they were of

[9] The numbers have the same values regarding the degree of haemolysis as with the *t.c.f.* reaction.

value; and at the same time they presented fewer difficulties for inclusion or exclusion of individual cases than other means of classification would have introduced. Before attempting an analysis of results in table 1 the following explanation regarding each group should be made:

The group designated *positive parenchymatous lesion* means that stereoscopic plates had shown an undoubted tuberculous lesion. On these cases an average of 1.5 stereograms were taken, and 114 were found to be minimal (including 5 miliary cases), 95 moderately ad-

TABLE 1

	POSITIVE PARENCHYMATOUS LESION (STEREOSCOPIC PLATE INTERPRETATION) (265 CASES)	CLINICALLY NONTUBERCULOUS (194 CASES)	CLINICAL NORMALS (77 CASES)
Average number of tests per case	2.52	2.10	3.0
	per cent	*per cent*	*per cent*
A: t. c. f. reaction:			
1. Positive* (in any test)	41.1 (109)	4.6 (9)	9.0 (7)
2. Weak fixation† (in any test)	48.3 (128)	50.5 (98)	57.4 (44)
3. Positive or weak fixation (in any test)	76.9 (204)	53.0 (103)	59.7 (46)
4. Negative (in all tests)	23.0 (61)	46.9 (91)	40.2 (31)
5. Negative (in any one test)	44.1 (117)	73.1 (142)	72.7 (56)
B: Inhibitive reaction:			
1. Positive (in any test)	*56.9* (151)	*11.3* (22)	6.4 (5)
2. Positive (in any 2 tests)	*18.1* (49)	1.5 (3)	0 (0)
3. Normal (in all tests)	43.0 (114)	89.6 (172)	93.5 (72)
4. Normal (in any test)	76.9 (204)	93.3 (181)	100 (77)
C: Combined reactions:			
1. Both positive (in any one test)	*33.2* (88)	5.1 (10)	0 (0)
2. Normal *i.* and less than positive *t. c. f.* (in all tests)	21.8 (58)	84.0 (163)	84.4 (65)

* *Positive* means the complete fixation of two *or more units* of complement.

† *Weak fixation* means the fixation of less than two units of complement.

vanced, and 26 far advanced. The final diagnosis was clinical tuberculosis, except in 12 cases in which *previously tuberculous* was diagnosed in 11 instances alone, this being coupled with *clinical tuberculosis arrested* as a secondary diagnosis in the twelfth case. Excluding these 11 cases, the further classifications made were 105 cases active, 75 quiescent, 50 apparently arrested, 23 arrested, and 1 apparently cured.

Under the heading of *final clinical diagnosis* in the questionnaire the following four subdivisions were employed: (a) *Clinically tuberculous*

or "accepted as" tuberculous: The circumstances of "accepted as" may be amplified as follows: A proportion of these patients already officially diagnosed as tuberculous showed no evidence of this and were in excellent health, which, if continued, resulted in a rapid advance of the subclassifications toward *cured.* With others suffering various degrees of debility, in whom no satisfactory evidence of tuberculosis could be found, every endeavor, including reference to other clinics or departments, was made to reach a satisfactory diagnosis, failing which they were carried as *tuberculosis suspect.* As all nonpulmonary forms of tuberculosis are referred to the clinic these are included in the 1000 cases reviewed, and together with the pulmonary forms total 665. (b) *Previously tuberculous:* This classification was necessary to provide for the occasional case in which, though the radiogram showed a positive lesion or the past history premised this, there were no clinical evidences of present disease. (c) *Suspect tuberculosis.* (d) *Nontuberculous.* In summarizing the histories occasionally a secondary diagnosis was added such as *b* (*c*), *d* (*b*), etc.

In the 194 cases diagnosed as nontuberculous an average of 1.28 stereograms were taken. In 28 cases tubercle as a possible factor could not be excluded and was added as a secondary diagnosis (*c*), in addition to an evident nontuberculous condition. Since the summaries were completed it has been noticed that a few in this group have shown tubercle to be a factor.

These remarks on the two groups (parenchymatous lesions and nontuberculous) have attempted to make it clear that while it is legitimate to consider practically all the former as clinically tuberculous, and nearly all the latter as nontuberculous, there is still a small and questionable percentage in both groups which will not conform to this rigid division. The data to be submitted on the *clinical normals* will show that neither can all of them be considered entirely nontuberculous.

In analyzing the results (table 1) it will be seen that the percentages in the two nontuberculous groups are in fairly close accord, and show usually less than a difference of 5 per cent, and are in any instance nearer 5 than 10 per cent. Regarding the results from a diagnostic point of view, the greatest difference between the tuberculous and the nontuberculous groups is obtained with a 2-unit degree of fixation, a positive inhibitive in one or two tests, and a combined positive result, that is, *A1, B1, B2, C1.* These four serological findings do not vary more than 5 per cent in their respective ratios between the tuberculous

and the nontuberculous. Approximately, then, they should have the same diagnostic significance. On the basis of the percentage findings, and failing evident tubercle, we believe that there is sufficient to warrant the statement that, when any one of these results is obtained, a satisfactory nontuberculous diagnosis should be found or the patient kept under observation as *suspect tubercle.*

The percentage of cases in which some lesser degree of fixation (*A2*) was obtained is extraordinarily close in each of the three groups. The division of the *t.c.f.* test results, into those fixing 2 units or more and those fixing less than 2 units, is arbitrary, but has seemed the most satisfactory for classification purposes. However divided, the results show that the diagnostic significance of the test rapidly diminishes with lessening degrees of positiveness below a 2-unit strength.

We feel that the general significance of changes in the serological results obtained by serial tests is as important as or even more so than the diagnostic value of a single test. This cannot be demonstrated graphically, and to be appreciated should be actually applied in the individual case. The differences in the results with such serological classification for any one or all tests (table 1) do show, however, that material changes are obtained.

Though it is anticipating our argument, the following generalizations may conveniently be given here:

Usually a positive *t.c.f.* reaction remains unchanged, and variations when they do occur are not sudden or marked. There is no consistency or clinical explanation for those definitely tuberculous who give a negative fixation. These negative cases, together with the nontuberculous in which varying degrees of fixation are obtained, constitute the weakness of the single *t.c.f.* test.

In contrast, the inhibitive test may vary considerably and at short intervals. Table 1 shows that in the tuberculous group normal results only were obtained in 43 per cent. This is not necessarily inconsistent with the type of progress in these cases. The appearance of a positive test, especially when unexpected, is what gives this test its chief value, as it suggests that activation of the disease may be expected. The instances in which this type of correlation is verified clinically have been sufficiently frequent to cause us to actively utilize the information therapeutically. This can be done by altering the ratio of rest and exercise, or by arranging for an earlier reëxamination. In the presence

of distinct clinical activity a positive inhibitive result lends a more favorable aspect to the case.

The extent to which we have found this method of interpretation to be of value in the routine examination and reëxamination of patients can be illustrated most concisely by referring to the parenchymatous group.

Of these 265 cases 151 gave a positive inhibitive reaction, associated with 53 cases giving a strong *t.c.f.* and 79 cases in which at least one test gave no *t.c.f.* In 88 cases combined positive reactions were obtained. The interpretation which we attach to the tests proved to be at one time or another the most pronounced of any feature of the examination in 60 cases. This means that in these 60 cases either (1) the diagnosis was indefinite by clinical examination alone but confirmed by radiological or sputum examination, or (2) the suggestion afforded by changes in serological results was *subsequently* confirmed by the clinical course of the disease. Of the 265 cases 114 gave persistently normal inhibitive reactions, associated with 56 cases in which a strong *t.c.f.* was obtained, and 36 cases in which at least one test gave no *t.c.f.* Taking the group of 114 as a whole, the tests were of no significance in 28 cases, were shown to be confirmed in varying degrees of importance by the clinical course in 83 cases, and were apparently misleading in 3.

An attempt has been made throughout this report to restrict the observations to such groups as should provide the clearest evidence either of the specific character of the tests or of their practical value. On these grounds cases of pleurisy with serous effusion seemed worthy of detailed study.

Table 2 gives the radiological and serological findings in 22 cases occurring in the 1000 reviewed. The very high percentage of positive inhibitive results is noteworthy, and to a considerable extent illustrates the two clinical features most frequently associated with its presence, namely, activity and favorable prognosis. The relative infrequency with which normal and positive inhibitive results alternate is, to a considerable extent, due to the number of cases (7) in which only one test was done.

Of the 11 cases, in which the stereoscopic plates failed to show a definite parenchymatous lesion initially or throughout the course of their observation, 9 gave a positive inhibitive reaction, 9 in at least one of their tests gave a negative fixation reaction, and only 3 in any of their

tests a positive *t.c.f.* of 2 units of complement. These 11 cases, in which X-ray confirmation is lacking, exemplify a type of involvement and a clinically favorable prognosis which would seem suitable to illustrate the value of the tests. The usually accepted tuberculous etiology of wet pleurisy is supported by the inhibitive reaction in 9 cases and by the *t.c.f.* reaction in 3 cases. The clinical characteristics of activity and this type of prognosis are those with which we have identified a positive inhibitive reaction when it is obtained in frank tuberculosis.

TABLE 2

22 cases of pleurisy with effusion

Average number of tests per patient	2.2
Maximum number in any one case	9.0
X-ray findings:	
Minimal	5
Moderately advanced	4
Far advanced	2
Presumably positive shadows	6
Negative or doubtful shadows	5

Serological tests

	per cent	
A: t. c. f. reaction:		
1. Strong fixation (in any test)	45.4	(10)
2. Weak fixation (in any test)	45.4	(10)
3. Negative (in all tests)	27.2	(6)
B: Inhibitive reaction:		
1. Positive (in any test)	81.8	(18)
2. Normal (in all tests)	18.1	(4)
C: Combined reactions:		
1. Both positive (in any one test)	50.0	(11)

Although 8 of the 11 cases failed to give a 2-unit degree of fixation, the lesser degrees of reaction may have been in satisfactory keeping with the clinical progress of the case. The number of negative *t.c.f.* tests is disappointing when considered diagnostically, particularly if only one test were taken.

Probably double the number of cases with serous effusion have been under observation by the clinic, but from a fairly close survey no material difference in the percentages obtained in these 22 cases would result had they been included. In one group of 4 cases seen in private practice

all gave a positive inhibitive reaction and, as well, all gave combined positive reactions in the same test.

A Review of 77 Clinical Normals

A. H. W. CAULFEILD AND CECILE COHEN

The group of cases designated *clinical normals* was obtained by calling for volunteers among the first-year medical students in January, 1921. Over 60 responded at once, subsequent additions, to replace those who for one reason or another dropped out, bringing the total to 77. During the winter and spring of 1921 all were given 0.05 mgm. of old tuberculin intracutaneously, and those who failed to react 0.5 mgm. some months later.[10] During that year serum was withdrawn in the majority twice and in all once, for the inhibitive and *t.c.f.* reactions. Stereoscopic plates were taken on all, either in the spring or early autumn of 1921.

Since that date one or two subsequent tests have been made each year, special pains being taken to repeat on all who showed in any test a positive *t.c.f.* with 2 units or more of complement, on all who had more than once given a positive *t.c.f.* of any degree, and on all who had given a positive inhibitive reaction. The coöperation of the students has, on the whole, been very remarkable, as is shown by the fact that, with an average of 3 tests per individual, there have been only 16 on whom the tests were done but once. Of these, 8 gave no *t.c.f.*, 7 a weak *t.c.f.*, and one a *t.c.f.* reaction of 2 units, the inhibitive reaction in all being normal.

It has been mentioned by Calmette and others that diphtheria antitoxin horse serum would fix complement with tuberculo-antigen. This fact has been repeatedly confirmed by us; and, in consequence, the possibility of natural diphtheria antitoxin acting as the cause of a positive *t.c.f.* reaction in human beings has presented itself.

To eliminate this possibility both Shick and Kellogg tests were done on 14 of this group, 12 of whom gave positive, and 2 negative results with both tests. Absorption tests with *K.L.* antigen on the 2 negative cases gave contradictory results, namely, one serum (*B.E.G. no. 1*)[11]

[10] The results obtained with the tuberculin tests were published in *The Journal, Canadian Medical Association*, September, 1922.

[11] These cases appear in table 3.

was unaffected by absorption; the other serum (*K.N.B. no. 17*)[11] showed no *t.c.f.* after absorption.

Contradictory results were also obtained with the absorption tests on the serum of the Shick-positive cases. The results obtained with the serum of one of these latter will serve to illustrate the conclusion reached, not only by work on this group but by tests carried out on the patient's serum and diphtheria antitoxin horse serum. A student (*T.N.F. no. 11*)[11] was both Shick and Kellogg positive. Before absorption, fixation of two units of complement was obtained, while after absorption there was merely a trace of fixation, the figures for the two results being 4000 and 1000.

There are reasonable grounds (as is shown later) for believing that this student is harboring living tubercle bacilli which have formed a demonstrable tuberculous lesion so that one would not expect absorption with *K.L.* antigen to have removed the antibodies responsible for the complement fixation obtained with the tuberculo-antigen. Further, as there was no constancy in the results obtained by absorption tests with either Shick-positive or negative sera, we have in consequence concluded that the presence of natural antitoxin cannot be regarded as an explanation of a positive *t.c.f.* reaction; nor would one be warranted in concluding that any *t.c.f.* reaction obtained was not specific if absorption with *K.L.* antigen should remove the *t.c.f.* antibodies.

To correlate the serial serological and X-ray studies, it seemed sufficient to repeat the stereoscopic films on (1) those who had shown a positive *t.c.f.* of 2 units or more of complement in any test, (2) those who had given a positive inhibitive reaction, and (3) those who had given a *t.c.f.* reaction of less than 2 units of complement in two or more tests. These cases, 21 in number, are summarized in table 3, although as yet the X-ray work has to be completed on eight of them.

The 13 "repeat" stereograms were carefully studied, and in any showing marked or suggestive shadows the original 1921 plates were drawn for plate to plate comparisons.[12] Ten of the 1924 films were entirely negative, or showed not unduly suggestive shadows which were found to be identical with those in the 1921 plates. In 3, however, both suggestive or positive shadows were obtained, in which the details of comparison are as follows:

[12] These plates were compared by means of Caldwell's prismatic stereoscope and suitable illuminating boxes, so that the comparisons were of stereoscopic views and not flat plates.

Student T.N.F. (no. 11, table 3) in the 1924 film showed, at the level of the 4th interspace posteriorly, a small intrapulmonary cluster which, on stereoscopic examination, presented the characteristics of a small parenchymatous lesion; the earlier plates failed to depict this small cluster, although the other shadows, largely peribronchial in type and in themselves not diagnostic, were practically identical. The 1924 plate is reproduced in figure 1.

TABLE 3

Results of serial tests on selected number of students

STUDENT	TOTAL NUMBER OF TESTS	T.C.F. REACTION*			INHIBITIVE REACTION		COMBINED POSITIVE IN ANY TEST
		Negative	Weak	Strong	Normal	Positive	
1. B.E.G.	5	—	2	3	5	—	0
2. B.W.B.	5	—	5	—	5	—	0
3. B.F.B.	4	—	4	—	4	—	0
4. C.H.S.	3	2	1	—	2	1	0
5. D.G.A.	4	1	3	—	4	—	0
6. F.F.J.	3	—	3	—	3	—	0
7. H.L.	5	—	—	5	5	—	0
8. L.P.F.	4	1	3	—	4	—	0
9. M.E.L.	5	3	2	—	4	1	0
10. P.H.A.	5	—	2	3	5	—	0
11. T.N.F.	5	—	1	4	5	—	0
12. V.R.P.	5	2	3	—	4	1	0
13. W.A.M.	4	1	3	—	3	1	0
14. B.W.W.	3	3	—	—	2	1	0
15. G.R.C.	5	2	3	—	5	—	0
16. G.J.R.I.	2	—	2	—	2	—	0
17. K.N.B.	5	—	3	2	5		0
18. L.J.L.	3	—	3	—	3	—	0
19. M.G.E.	5	1	4	—	5	—	0
20. P.D.	3	—	2	1	3	—	0
21. V.G.E.	1	—	—	1	1	—	0

* "*Weak*" means that less than 2 units; "*strong*" that 2 units or more of complement were fixed.

† "Repeat" stereograms have been taken on nos. 1 to 13.

Student W.A.M. (no. 13, table 3) in the 1924 films showed fairly gross shadows which, though suggestive of a tuberculous etiology, could not be regarded as indicative of more than some infectious process. Comparison between both sets of stereograms showed, in each, the identical shadows. This plate is reproduced in figure 2.

Student C.H.S. (no. 4, table 3) in the 1924 films showed shadows practically confined to the hilum regions, and was the least suggestive

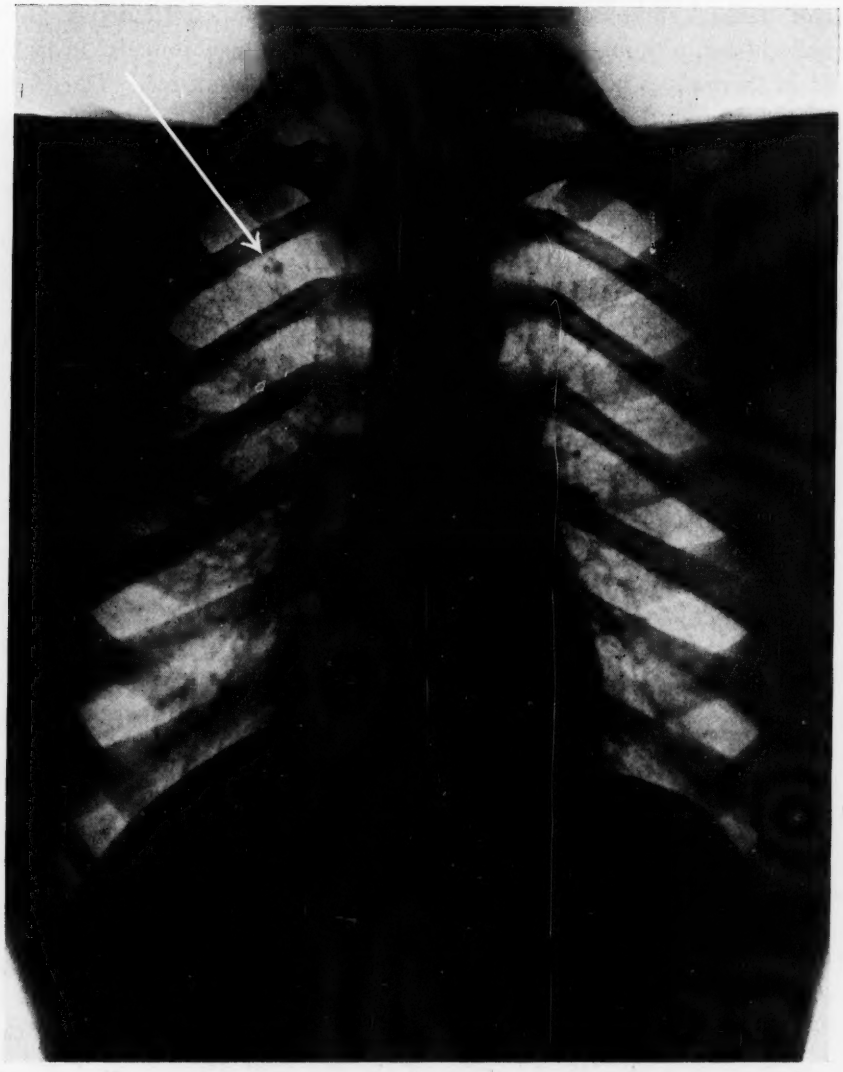

FIG. 1. CASE T.N.F. (NO. 11, TABLE 3)

of the three. The original plates unfortunately could not be found for exact comparison.

From the clinical point of view all the students have been subjected

to the routine University Medical Service examination once or oftener. Sixty-three have been classified as fit (*A1*); 14 were put in lower cate-

FIG. 2. CASE W.A.M. (NO. 13, TABLE 3)

gories, *A-2*, *B*, etc., for various medical reasons. All of the 21 cases in table 3 were classified as *A1* except 4, three of which were lowered on account of some cardiac condition and one on account of poor weight

and development. These 4 students are nos. 6, 7, 8 and 18 (table 3). In other words, in none of the 12 "suspects" on serological grounds was there a suspicion of tubercle on routine medical examination.

Special examination of student T.N.F. after the second X-ray revealed the fact that one of his family had died two years before of tuberculosis. He himself felt rather easily tired, but this could be explained on the grounds of his studies and late examinations. Physical examination was negative, and although he had noticed a certain irregularity of pulse he had not taken his temperature. The examination of W.A.M. showed a young man (aet. 24) apparently the picture of health, of excellent development and with normal physical findings. His past history was clear, and there was no evidence that he had suffered from any type of pulmonary disease to explain the radiographic findings. After considerable questioning the fact that a brother was ill with tuberculosis of the kidney was elicited. The third case (C.H.S. aet. 24) was in the best of health and gave in every way normal physical findings. His past history was free from any evidence of disease, pulmonary or otherwise, or any known exposure.

An analysis of the serological results in table 3 shows that in 7 cases a positive *t.c.f.* of 2 units of complement was obtained in one or more tests, and a single positive inhibitive reaction in 5 cases. Of these latter all but one gave a *t.c.f.* reaction of less than 2 units of complement once or oftener.

These 12, from the serological point of view, may be regarded as needing in varying degrees the exclusion of tubercle; and more particularly so had they been patients, that is, had they presented symptoms or physical signs and were not supposedly normals. On 8 of these, "repeat" stereograms have been taken, with the result that one has apparently developed during the years of investigation a small, but demonstrable (by X-ray) pulmonary lesion; in two others shadows were found which may be regarded as compatible with a tuberculous etiology, even though these have remained unchanged, as shown by comparison of the more suggestive sets of plates.

The past history of exposure (as a third indication) supports the probability of a tuberculous lesion in two of these. In compiling percentage findings with these students as a group of normals, it would in consequence seem legitimate to delete 2. This would reduce the percentage of positive *t.c.f.* reactions to 7.7 per cent, and the percentage of positive inhibitive reactions to 5.3 per cent.

Except to note that in these approximate percentages the serological

results are obtained without explanation in clinical normals, the use of actual figures may suggest a false value. Serological tests afford no clinical diagnoses but suggestions which should be eliminated or confirmed clinically by other methods.

In the remaining 10 serological suspects, continued tests, combined with other methods of observation, should show whether the results previously obtained were due to laboratory error or the extent to which the lesion should be regarded as an infection or as a disease.

Reference here seems appropriate to the after-results obtained in a group of previously published (6) (10) normals. Out of a group of 18, positive inhibitive tests were obtained in 2 cases, neither of which showed any indication of tuberculosis. One of these (no. 12 of that publication) developed tuberculous orchitis while on active service during the late war. Since then his recovery has persisted, and both tests have remained negative.

A Review of Contacts with Cases of Open Tuberculosis

A. H. W. CAULFEILD AND W. E. OGDEN

In following our cases of tubercle by means of serial serological tests it was observed, among those progressing favorably and as the months increased from 12 to 24 or 36 or more, that the occurrence of a positive inhibitive test became more and more rare. In somewhat similar fashion, though later, the degree of the *t.c.f.* reaction would, as a rule, lessen, and weakly positive results would be interspersed with negatives.

If our interpretation is correct (and these tests do provide a more sensitive index regarding the permanence of a cure, as apparent clinically) likewise, but in reverse fashion, the tests should be of significance at the time of onset, such as might be expected to develop among those exposed to open cases.

As a group, the contacts seen in private practice seemed to furnish a fuller type of observation than those encountered in the clinic, and on this account they have been chosen. In number 84, they comprise only known exposures to open cases and in the majority are "family contacts." As might be expected, the degree of completeness of the observation has depended to a large extent upon the attitude of the contact. In consequence, as many tests and radiograms have not been taken as might have been advisable. Usually, with the blood withdrawal, it has been found most feasible to get the history and a physical examination if this was in any degree suggestive, or to leave

the physical examination until the serological report was available, when the desirability of radiographic work could be more definitely emphasized. It is frequently easier to get a contact to report periodically for a few moments' interrogation and a "repeat" blood test than it is to get him to submit to a second physical or radiographic examination. In many instances this is a fully satisfactory method of following the case.

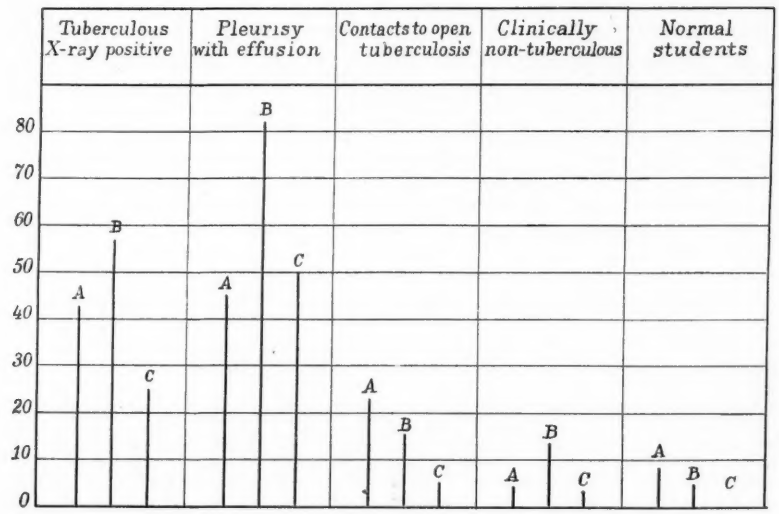

CHART 1

A = positive t.c.f. reaction (2 units of complement or more) in any one test.
B = positive inhibitive reaction in any one test.
C = combined positive reaction in any one test.

In chart 1 the percentage findings of the three more important serological results are shown for all the different groups dealt with in this report. These, while considerably less than the results obtained with the clinically tuberculous, are higher than the percentages obtained in the nontuberculous and normal group. This is more marked with the *t.c.f.* reaction than with the inhibitive test, which seems in logical sequence with their respective significance. In greater detail, and to compare with table 1, the following results were obtained:

(1) *Positive t.c.f.*, of 2 units or more in any test, 21.4 per cent (18); of less than 2 units, 52.1 per cent (44); of any degree, 64.2 per cent (54).

(2) *Negative t.c.f.*, in all tests 35.7 per cent (30); in any one test 60.7 per cent (51).

(3) *Positive inhibitive*, in any test, 15.4 per cent (13); in more than one test, 3.5 per cent (3).

(4) *Normal inhibitive*, in any test, 97.6 per cent (82).

(5) *Combined positive*, in any one test, 5.9 per cent (5).

The 40 cases in which stereograms have been obtained once or oftener include all those who were willing to have these taken, as well as most of those whose investigation furnished any suggestion that implantation might have taken place as a result of their exposure. From a serological point of view 5 cases giving a positive inhibitive test and 4 cases giving a strong *t.c.f.* reaction were not X-rayed but continued under observation, allowing repeated tests.

The radiograms have been classified as follows:

A: Those showing characteristically positive parenchymatous shadows: 5, or 12.5 per cent of those X-rayed: (a) minimal in extent, 2; (b) moderately advanced in extent, 3.

B: Those showing slight shadows, to be regarded as parenchymatous and under any circimstances as probably tuberculous: 8, or 20.0 per cent.

C: Those showing shadows of peribronchial, lymph-node, or pleural location, which it seemed legitimate to regard with suspicion: 10, or 25.0 per cent.

D: All others: 17, or 42.5 per cent.

The positive serological findings are not predominantly found in any of the radiological classifications adopted, which on first impression might appear to support a criticism of their value. This would be true were clinical tubercle the legitimate or logical interpretation of a positive test. We are endeavoring in these reports to produce evidence that they have a clinical value when interpreted differently. We believe a positive result with either test need never necessarily mean clinical tuberculosis, but a positive *t.c.f.* test suggests that a definite lesion is present, while a positive inhibitive test is an indication of some phase of immunity due to the active presence of bacilli within the host. Estimating the correctness of these indications from the percentages obtained in the tuberculous and nontuberculous, they would at least be as 8 to 1.

Of the 5 cases of minimal or moderately advanced involvement 3 gave a strong degree of *t.c.f.* (2 units or more) and 1 a positive inhibitive test. Two of the former were easily diagnosed by ordinary clinical methods, the third only being detected by radiological examination

after this was indicated because of the serological findings. This patient failed during her period of observation (2 years) to show any clinical evidence of the disease and has continued to lead a fairly strenuous life.

To illustrate why the real value of the serological findings may be masked if judged by the percentages obtained in the different radiological classifications, the following history is detailed:

H. L.: A 12-year-old boy, contact to a tuberculous mother, was examined in 1919, and gave a slightly suggestive history, though the physical signs were negative. The serological results were a positive inhibitive and a weakly positive *t.c.f.* test. The X-ray could not be classified as other than normal, despite a slight and questionable accentuation of the bronchial shadows on one side. After a beneficial stay in a preventorium he started to work, and has continued without any evidence of definite ill health ever since. Subsequent plates in 1922 showed what appeared to be a hilum lymph-node enlargement, but this by itself could not be considered as particularly suggestive except for the previous plates and past history. The four subsequent tests have given variations above and below a 2-unit degree of *t.c.f.*, and the inhibitive reaction has remained normal. More frequent tests might have shown variations in the inhibitive reaction. The plates cannot be classed higher than *C*, and some hesitancy was felt in selecting this classification rather than *D*.

As regards disposal: 4 have been put for a varying period on active treatment; 17 have submitted to some change in their day's work or exercise, or have taken a short afternoon rest; 42 have continued their usual mode of life, reporting at various intervals for some type of examination, if only a short interrogation and a "repeat" blood test. In many of these latter we already feel that the possibility of disease has been excluded; in others there are various reasons for continuing the observations. Twenty-one have not reappeared or have not done so for a considerable period of time.

Probably because of the incompleteness of our observation on a considerable number, the percentages obtained (chart 1) may be misrepresentative. Even the period of observation has been too short, especially if one is to judge by what data are available on the admittance to sanatoria of patients widowed through tuberculosis of their consorts. Barnes (11) finds the average period of time between death of the consort and admittance to be 4.5 years. Of our 84 cases, 19 were first seen in 1924, the first case coming under observation in 1919, and the remainder between those years.

Limiting the analysis to those on whom 2 or more tests have been done, there are 42 cases with an average of 3.2 tests. Of these, 18 gave either a positive inhibitive, a 2-unit degree of fixation, or both. Interpreted from a serological point of view, this means that of 42 contacts seen more than once 42.8 per cent should be fully investigated, and, even though careful clinical methods fail to demonstrate cause for suspicion, they should be kept under observation as likely instances of implantation due to their exposure.

In the remaining 57.1 per cent (those giving repeated normal inhibitive tests, together with negative or but weakly positive *t.c.f.* reactions) a lesion can be regarded as unlikely, provided at the same time careful clinical examination fails to demonstrate this. In such cases we believe the possibility of the later development of tuberculosis to be practically excluded. Even with the comparatively few contacts under observation the truth of this conception has been repeatedly proved in those cases developing unrelated nontuberculous conditions which symptomatically suggested at certain stages possible tubercle.

If our interpretation is correct, the tests furnish a truer indication of the degree in which exposure has resulted in implantation as a latent tuberculosis than is to be obtained by other methods. Probably the above noted percentage of 42.8 is nearer the truth than any given in chart 1.

The importance, to both the contact and the community, of correctly estimating the possibility of later disease as a result of exposure will be granted by all, as well as the frequency of negative findings by clinical and radiological examinations. If to these methods serial tests are added, further individual data are obtained, which we believe will aid to an inestimable degree in controlling the subsequent development of clinical tuberculosis. An approximate comparison of the value of serial tests in contacts is afforded by the use we make of the tuberculin test in children.

Discussion and Summary

The clinical value of serial tests, taken during the treatment and observation of tuberculosis cases, can only be properly appreciated by comparing chronologically the variations in the serological results and the clinical changes. Distinct variations do occur in both tests; with the *t.c.f.* these are usually slight and take place slowly, but with the inhibitive test they may be sudden and varied. The inadequacies of

our methods of clinical classification increase the difficulties encountered in attempting to graphically present correlation between the variation obtained by the combined serological and clinical changes in any large number of cases.

In our experience the indications given by repeating the tests predicate, sufficiently frequently, later clinical changes, so that their significance cannot be safely ignored. Even though a marked serological variation may not always be verified clinically, the results of all the tests actually aid one in classifying the case regarding activity, quiescence, etc., and in the estimate of work tolerance, that is, prognosis. Perhaps the most striking feature, which has occurred repeatedly, has been a positive serological finding at the initial examination which was otherwise unsuggestive regarding tubercle, and the later clinical development of the disease, months or a year or so after the initial examination, that is, diagnosis. This has occurred more frequently with an initially positive inhibitive than with a positive *t.c.f.* test. The extent in which both the prognostic and diagnostic indications of the tests have been subsequently verified clinically is summed up in the percentages given regarding the correlation between the results of the tests and the clinical progress observed in the 265 cases of tuberculosis.

Selected cases could easily be cited, but this method of demonstration is tedious to read and space-consuming. Moreover we feel that such examples are unconvincing, as they give the impression that only favorable cases were selected, that others were overlooked, or that the clinical work was poor or hampered by inadequate investigation in all cases.

Undoubtedly the proper evaluation of two serological tests, which we believe have both practical diagnostic and prognostic value, is as difficult and as full of pitfalls as the evaluation of a specific remedy which, let us grant, may help but not dramatically cure the disease. This we fully recognize. The claim of a therapeutic aid has inducements that methods of diagnostic and prognostic value, important though they may be, lack. It has seemed, however, that a fundamental basis might be struck if the combined tests were carried out on groups, widely divergent as regards the likelihood of either clinical tuberculosis or a pathological lesion not clinically active. This has been the method chosen and the percentage results obtained with both tests have been given in the different tables and the chart.

Tuberculosis is regarded as a disease and an infection, but this classification only indicates the extreme ends in a line of thought. Our defini-

tion of just what is disease, and what is infection, is vague, especially where they begin to overlap. The use of the term "latent" is an attempt to show where infection ends and disease begins.

Theoretically, and it is confirmed experimentally, it is just as reasonable to obtain a positive serological test in certain stages of an infection or during latency as it is during disease. Graphically speaking, infection or latency may approach or recede from disease, eventually reaching or missing the status of that clinical condition. The resulting biological reactions between bacilli and host are as likely to give variations in the serological reactions, whether or not sufficient symptoms or physical signs result for a clinical diagnosis to be made. Unfortunately for the practical value of the *t.c.f.* test, it is not reasonable to regard all positive findings among individuals in whom no disease can be demonstrated, as examples of infection or "latency," as we may with a positive tuberculin reaction. Such an interpretation seems unreasonable, partly on account of the closely approximating percentage findings (*A2*, table 1) in those three groups and the contacts, and partly because the test is so frequently absent in all types of the clinical disease. As shown in table 1, 23 per cent of the tuberculous failed to show in any test a positive *t.c.f.* result, and in 44 per cent of these cases a negative result was obtained in at least one of the tests.

However, if a distinction in the degree of positiveness is made, table 1 shows that a strong fixation (that is, a 2-unit result or better) is sufficiently rarely found in the essentially nontuberculous groups to give such a finding extreme significance diagnostically—greater significance than the percentages tabled because of the probability and demonstration of "latency" in these cases as discussed under the nontuberculous and normal groups. The deletion of these particular cases reduces the percentage in both nontuberculous groups to nearer 5 than 10 per cent, and is to be contrasted with the 41.1 per cent in the tuberculous. As a rider to the 41.1 per cent finding is our interpretation that a lesser degree of fixation was satisfactory, and in better correlation with the clinical type and progress in many of the remaining 58.9 per cent (that is, 100 per cent less 41.1 per cent).

The percentages obtained in the three classifications adopted for the results of this test (table 1) show that the test must change considerably. It would seem logical to regard a lessening in the degree of positiveness as undoubtedly of favorable omen provided there is no definite clinical evidence to the contrary. This has been our observation; and although instances have occurred in which the degree has not

decreased with "continued arrest" or "apparent cure" this has been the exception rather than the rule, and such exceptions are most frequently found in the cases with extensive pathological involvement.

With the inhibitive test an entirely different interpretation is to be applied. Our experience has taught us to regard "normal" results (that is, negative or third-class) as entirely reasonable, and to be expected in at least two phases of the definitely tuberculous as well as in the normal. If obtained in the tuberculous with, for instance, fever and malaise, we believe the prognosis to be poor, although it has the reverse significance if, so to speak, the case is arrested, is without fever and is doing well, or is even holding its own. The persistence, therefore, of normal tests is to be regarded as favorable unless there is definite evidence to the contrary. In the normal students, normal inhibitives were obtained in close to 100 per cent of the individuals tested —over 96 per cent if those normals are excluded in whom there are reasonable grounds to concede a demonstrable anatomical lesion. In the same way there must be correlation between the general condition of the patient and a positive inhibitive test in the interpretation of this serological finding. If there is definite clinical exacerbation (fever and malaise, for example) such a serological result lends a favorable prognostic aspect, but does not necessarily mean that the patient must recover and complete an apparent cure. The same finding in the absence of clinical activity calls for reduced exercise, or at least an earlier reëxamination, as in itself the serological finding indicates biological activity, and likely therefore in the majority of instances to be clinically evident later.

If no specific interpretation is to be attached to a positive inhibitive test, there is no explanation why it should have been obtained in the radiographically positive cases in a higher percentage than the 2-unit degree of complement fixation and in the cases of pleuritic effusion in a higher percentage than all degrees of the *t.c.f.* reaction.

Respectively, these findings of 56.9 per cent (*B1*, table 1) and 81.8 per cent (table 2) should be contrasted, not with the tabled results in the nontuberculous cases and normals of 11.3 per cent and 6.4 per cent, but with the amended percentages because of fair proof, on other grounds, of tubercle. In the nontuberculous this has not been worked out, but with the normals it is at least 5.3 per cent. As with the 2-unit or more *t.c.f.* test, it is probably nearer 5 than 10 per cent.

The exclusive value of repeated normal inhibitive results, together with negative or alternating negative and weak *t.c.f.* reactions, is best illustrated in the two nontuberculous groups of table 1. In both

groups these serological findings were obtained in more than 84 per cent (table 1 as amended).

The significance of parts of chart 1 should also be modified as a result of an analysis of the data on contacts. Reasons were presented for regarding, on the basis of the serological findings, the figure of 42.8 per cent as an approximate estimate of the number who had suffered as a result of their exposure, that is, had received an implantation of bacilli from the open case. While this number of cases (18) is to be contrasted with those giving evidence on other grounds of tuberculosis (5), it should as well be criticized or considered in relationship to the corresponding serological results obtained in those groups as detailed in table 1, and subsequently modified by detailed analyses. The difference between 100 per cent and the percentages given under *C2*, table 1, correlates with the 42.8 per cent for the contacts. Otherwise expressed, the serological results point to a possible tuberculosis in the tuberculous cases in 78.2 per cent, in contacts in 42.8 per cent, in nontuberculous cases in 16 per cent, and in normals in 15.6 per cent. As a rider to the tuberculous cases, the serological results in many of the 21.8 per cent of cases (that is, 100 per cent less 78.2 per cent) were more in keeping with the clinical condition and progress than would have been a positive inhibitive or a positive *t.c.f.* result,—as we interpret them. The percentages in both nontuberculous groups (16 and 15.6 per cent) should be reduced because of legitimate deletions as already explained; with the normal students this is at least 12.9 per cent.

To our knowledge, no paper has appeared dealing with the value of serial serological tests. The weaknesses inherent to the single *t.c.f.* reaction from a diagnostic point of view (and thereby the cause of controversy) frequently show up as clinical assets when carried out serially and interpreted not too literally. The inhibitive test has not been tried except in a few laboratories in Ontario. To us there seems sufficient evidence to believe that the two tests depict, as perhaps an imperfect mosaic, certain of the immunological phases, which can be interpreted clinically; and are helpful in categorizing the patient's past progress, present condition, and temporarily his prognosis.

With regard to the general problem of tuberculosis rather than the individual, the chief value of serial tests would seem to lie in their application to contacts. The possibility of reducing materially the later development of clinical tuberculosis in such individuals should warrant a trial of the tests in any public health department, already engaged in an adequate control of its open cases.

SUMMARY

1. The results obtained by carrying out two serological tests periodically during several years' observation on "normals," contacts and cases of tuberculous and nontuberculous disease have been classified and given in percentages. From these an approximate diagnostic value can be drawn.

2. Among the normals there was serological evidence for suspecting the presence of a tuberculous lesion in 12, and this was subsequently confirmed in 2 by at least two other methods of investigation.

3. Among the contacts there were similar grounds for suspecting that the exposure had resulted in an implantation of the bacilli in over 40 per cent.

4. Among the cases the tests were helpful in estimating the probability of tuberculosis as a correct diagnosis, and among the definitely tuberculous in visualizing the progress frequently before there were appreciable clinical evidences of a change in the course of the disease.

5. The tests will not give a satisfactory short cut (laboratory) diagnosis for or against tuberculosis. If this is demanded the results will be disappointing or misleading because (*a*) the *t.c.f.* reaction is negative in a considerable percentage of the tuberculous, (*b*) because it is at least weakly positive in a large number who are evidently not tuberculous, (*c*) because the inhibitive test can consistently be normal in a large percentage of the definitely tuberculous, and (*d*) because an occasional case will give a positive inhibitive test in which there will be no grounds for suspecting clinical tuberculosis.

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ABSTRACTS OF TUBERCULOSIS

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Treatment of Tuberculosis with Sanocrysine.—Sanocrysine is auro-sodium-thiosulphate, $Au(S_2O_3)_2Na_3$. Holger Moellgaard, Professor of Physiology in the Veterinary School at Copenhagen, has found that his compound has a specific therapeutic effect against tuberculosis, killing tubercle bacilli *in vivo* as well as *in vitro*. It is of comparatively little toxicity; 60 mgm. may be injected in normal men and animals without producing any effect. The tolerance of guinea pigs is somewhat smaller, about 30 mgm., but in mice as much as 120 mgm. per kg. may be injected. The therapeutic dose is never higher than one-third of the tolerated one, namely, 10 to 20 mgm. per kg. In man 0.5 to 1 gm. is injected for therapeutic effect. After such injections gold can be traced in the urine during six days; it is assumed that after this time the excretion is complete. The substance rapidly diffuses through animal membranes almost as well as iodides. Sanocrysine in a concentration of 1 to 100,000 stops the growth of tubercle bacilli if added to a medium containing the bacilli. If virulent bacilli are washed twice within 24 hours with a 1 to 100,000 solution most of the bacilli are killed. If washed with a 1 to 1000 solution the bacilli have lost their stability toward acids and can no longer be stained by the usual methods. Upon injecting sanocrysine into calves which were experimentally infected with tubercle bacilli, violent reactions were observed: edema of the lungs, albuminuria, hyperthermia and also hypothermia, leading invariably to the death of the animals within a few days. This is due to the endotoxins (tuberculin) contained in living bacilli and liberated when they are killed by sanocrysine. Every attempt to kill tubercle bacilli by means of chemotherapeutic agents will have to meet this difficulty. In order to make use of the curative action of sanocrysine, a means had to be found which could neutralize these endotoxins. For this purpose Moellgaard prepared an antituberculin serum by injecting calves with dead tubercle bacilli and tuberculine for weeks and months, until these animals exhibited a high immunity, as shown by complement fixation. By injecting such a serum at the same time with or shortly after sanocrysine, splendid therapeutic results were obtained in calves, artificially infected by inoculation of 20 mgm. of tubercle bacilli intravenously. The antituberculin serum proved quite efficient in curing the tuberculin shock produced by sanocrysine in these tuberculous animals. After killing the animals thus treated, some time later, no trace of tuberculous infection can be found in any organ, while in infected control animals the lungs are full of tubercles. Similar experiments were performed with rabbits and goats. In guinea pigs they cannot be performed, as these animals are too sensitive toward sanocrysine, the kidneys being affected. In spontaneous tuberculosis of cattle a similar treatment proved insufficient, owing to fibrous, caseified and calcified foci, which are not accessible to the drug. No considerable change is brought about in this form of the disease. Before starting the treatment of human lung tuberculosis, Moellgaard tried the treatment on two tuberculous monkeys obtained from the Zoological Garden at Copenhagen. He succeeded in perfectly curing these animals, in the way described. Upon proceeding to the treatment of human cases, the same difficulties were experienced, as were observed in animals infected with tubercle bacilli. Unfortunately, in men the tuberculin shock following the sanocrysine injection can be prevented only imperfectly by the antituberculin serum. The intoxication disappears only partially after administering the serum because the mixture of tuberculin and anti-